Guidelines on the Use of Therapeutic Apheresis in Clinical Practice–Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

Zbigniew M. Szczepiorkowski,[1*†] Jeffrey L. Winters,[2*] Nicholas Bandarenko,[3*] Haewon C. Kim,[4*] Michael L. Linenberger,[5*] Marisa B. Marques,[6*] Ravindra Sarode,[7*] Joseph Schwartz,[8*] Robert Weinstein,[9*] and Beth H. Shaz[10*]

[1]Transfusion Medicine Service, Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire
[2]Division of Transfusion Medicine, Mayo Clinic, Rochester, Minnesota
[3]Transfusion Service, Department of Pathology, Duke University, Durham, North Carolina
[4]Apheresis Service, Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
[5]The Department of Medicine, Division of Hematology, University of Washington, Seattle, Washington
[6]Division of Laboratory Medicine, Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama
[7]Transfusion Medicine and Coagulation Laboratory, University of Texas, Southwestern Medical Center, Dallas, Texas
[8]Transfusion Medicine and Cellular Therapy Section, Department of Pathology and Cell Biology, Columbia University Medical Center, New York, New York
[9]Division of Transfusion Medicine, Department of Pathology, University of Massachusetts Medical School, Worcester, Massachusetts
[10]Center for Transfusion and Cellular Therapies, Department of Pathology and Laboratory Medicine, Emory University, Atlanta, Georgia

The American Society for Apheresis (ASFA) Apheresis Applications Committee is charged with a review and categorization of indications for therapeutic apheresis. Beginning with the 2007 ASFA Special Issue (fourth edition), the subcommittee has incorporated systematic review and evidence-based approach in the grading and categorization of indications. This Fifth ASFA Special Issue has further improved the process of using evidence-based medicine in the recommendations by refining the category definitions and by adding a grade of recommendation based on widely accepted GRADE system. The concept of a fact sheet was introduced in the Fourth edition and is only slightly modified in this current edition. The fact sheet succinctly summarizes the evidence for the use of therapeutic apheresis. The article consists of 59 fact sheets devoted to each disease entity currently categorized by the ASFA as category I through III. Category IV indications are also listed. J. Clin. Apheresis 25:83–177, 2010.   ©2010 American Society for Apheresis

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INTRODUCTION

We present you the American Society for Apheresis (ASFA) Special Issue 2010 (also known as the Fifth Edition of the ASFA Special Issue) with great pleasure. After more than five years of engaging work and the introduction of significant changes to the ASFA Special Issue, we believe that this document will appeal to practitioners of apheresis medicine. This is the second step in evidence-based ASFA categories, which includes analysis based on the quality of evidence and as well as the strength of recommendation derived from this evidence; the first step was publication of the ASFA Special Issue 2007 [1–3].

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*All authors contributed equally to this work.
†Correspondence to: Zbigniew M. Szczepiorkowski, MD, PhD; Transfusion Medicine Service, Department of Pathology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA. E-mail: ziggy@dartmouth.edu

TABLE I. Indications for Therapeutic Apheresis—ASFA 2010 Categories[a]

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. [Example: plasma exchange in Guillain-Barré syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition].
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. [Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease]
III	Optimum role of apheresis therapy is not established. Decision making should be individualized. [Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure].
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. [Example: plasma exchange for active rheumatoid arthritis].

[a]The description of the ASFA categories have been amended and simplified in comparison to the Third and Fourth Edition of the Special Issue [1,16]. Category P, which was introduced in the Fourth Edition, has been eliminated.

TABLE II. Level of Evidence Used in the ASFA Special Issue 2010[a]

Evidence level	Evidence quality
Type I	Obtained from at least one properly designed randomized controlled trial
Type II-1	Obtained from a well-designed controlled trials without randomization
Type II-2	Obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
Type II-3	Obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
Type III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

[a]Adopted from the criteria used by the University HealthCare Consortium [6].

This evidence-based approach is designed to achieve several objectives. First, it provides uniformity to category assignment and disease discussion while minimizing personal bias; second, it provides the strength of recommendation; and last, it provides comprehensive, yet condensed, information which could be shared with patients and clinical services requesting the use of therapeutic apheresis.

This article is a compilation of all fact sheets for disease entities, which were assigned ASFA categories I, II, and III, with one exception of burn shock resuscitation, which was assigned category IV. Because none of the diseases or data supporting the previously assigned category IV have changed since the Fourth ASFA Special Issue, the reader is referred to the previous article and to the table summarizing all indications [3].

Therapeutic apheresis procedures considered in this publication and included in the fact sheets are therapeutic plasma exchange (TPE), erythrocytapheresis/red blood cell (RBC) exchange, thrombocytapheresis, leukocytapheresis, extracorporeal photopheresis (ECP), immunadsorption (IA), selective removal methods, adsorptive cytapheresis, and membrane differential filtration.

METHODOLOGY

Evidence-Based Approach

We attempted in the ASFA Special Issue 2007 to incorporate evidence-based medicine into the well-defined and widely accepted ASFA Categories [2]. In the ASFA Special Issue 2010, we have added the quality of recommendation and modified the categories. This modified approach incorporates the categorization (Table I); quality of the evidence (Table II); and strength of the recommendation (Table III).

ASFA Categories

The definition of the four ASFA categories has been updated in the Fifth Special Issue from previous years (Table I). Changes in categorization occurred secondary to the addition of the strength of recommendation, which allowed categorization to be better aligned with the strength of the evidence and the quality of the literature. For example, the subcommittee could determine that an indication was Category I, such that apheresis is the accepted first-line of therapy, without requiring type I (randomized controlled trials) evidence. Category II now designates second-line therapy, and therefore, a patient must fail or be unable to undergo the first-line therapy. The definition for Category III has been also significantly changed to better reflect the individualized character of decision making process for diseases in this category. It is this committee's conviction that the recommendation grade and individual patient's clinical circumstances should guide inclusion of therapeutic apheresis in the treatment plan for Category III indications. The definition of category IV has also been clarified to underscore the

TABLE III. Grading Recommendations Adopted from Guyatt et al. [13]

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCT: randomized controlled trial.

importance of analysis of risks and benefits as well as the published evidence to determine if treatment with therapeutic apheresis is in the best interest of the patient. Category P has been eliminated in the current Special Issue and all previous diseases with category P in the Fourth Special Issue, namely dilated cardiomyopathy, inflammatory bowel disease, and age-related macular degeneration have been assigned other ASFA categories [2].

Quality of Evidence

There are various systems to evaluate the level of evidence [4,5]. We adopted the evidence quality criteria defined by the University HealthSystem Consortium (UHC) for the sole purpose of assessing the type of available evidence (Table II) [6]. We used the same system in the Fourth Edition of the ASFA Special Issue.

Grade of Recommendation

The committee recognized that ASFA categories alone even enhanced by the type of evidence and systematic review of the literature as presented in the ASFA Special Issue 2007 are still difficult to translate into clinical practice. This challenge has been an issue for many groups working on clinical recommendations and guidelines. Over last several years there has been a concerted effort to generate a system, which better translates the existing evidence to treatment of the individual patient. Several organizations implemented the Grading of Recommendations Assessment, Devel-

opment and Evaluation (GRADE) system for grading evidence. The system is generally user friendly as shown in multiple publications [7–11]. Furthermore, the American College of Chest Physicians uses this approach to evaluate therapeutic recommendations, most recently recommendations for the use of antithrombotic agents [12,13]. We have adopted the GRADE system to assign recommendation grades for therapeutic apheresis to enhance clinical value of ASFA categories. Table III contains abbreviated principles of grading recommendations derived from Guyatt et al. [13]. It is important to understand that the grade can be used in support and against the use of any particular therapeutic modality. Hence, weak recommendations, such as Grade 2C, are more likely to be affected by additional evidence of higher quality than strong recommendations based on high quality of evidence (e.g., Grade 1A).

The quality of published evidence can be affected by a number of factors [13]. For example, the quality of evidence based on a randomized controlled trial (RCT) can be decreased by poor quality of planning and implementation of the available RCTs suggesting high likelihood of bias; inconsistency of results; indirectness of evidence; and/or sparse evidence. Similarly, the quality of evidence based on observational studies can be increased by large magnitude of effect; all plausible confounding would reduce a demonstrated effect; and/or dose-response gradient. The members of the subcommittee were encouraged to take these variables into consideration.

Fig. 1.   Explanation of the fact sheet used in the ASFA Special Issue, Fifth Edition (2010).

A   The name of the disease as well as its eponym when appropriate.
B   This section lists the incidence and/or prevalence of the disease in the US and other selected geographic regions, when appropriate. In some instances when the incidence varies between genders, ethnicity, or race this information was noted as well. For certain diseases with insufficient data on either incidence or prevalence, other terms, such as rare or unknown were used. The reader is cautioned to use this information only as an indicator of disease prevalence. For some diseases, prevalence may vary by geographical area.
C   The type of therapeutic apheresis procedure is listed here. Only diseases, which were categorized, are listed. For certain diseases there are several apheresis based modalities available. In such instances (e.g., cardiac allograft rejection) all types of therapeutic apheresis procedures are listed.
D   Recommendation grade is assigned to each categorized entity. As noted in the text the authors of this research used the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for grading clinical recommendations level. For example, Grade 1B implies strong recommendation based on moderate quality evidence, whereas 2C refers to weak recommendation based on low or very low quality evidence. It is important to note that for category IV indications; this grading system would imply that category IV indication with Grade 1A has a strong recommendation against the use of TA supported by high quality evidence.

Fig. 1.   (*Continued*)

E   The ASFA category is listed for each therapeutic apheresis modality discussed. Some categories have additional information to further specify a subgroup of patients for whom the category was assigned. It is important to recognize that only in this particular subset of patients an ASFA category was assigned. More information is always available in the text of the fact sheet.

F   This section lists the number of patients reported in the literature who were treated with therapeutic apheresis. The committee used three categories fewer than 100, between 100 and 300, and more than 300, This entry will help readers in judging how often this entity was reported to be treated with TA, However, the number of patients treated is less important than the quality of the scientific reports and sometimes can be misleading as negative results tend to be published less frequently.

G   This section is used when there are several different TA procedures used and it was necessary to subdivide available scientific reports; as well as in the situation when different subset of patients are being analyzed. Not all entries will have this section.

H   Randomized controlled trials (RCT). The number of randomized controlled trials and the total number of patients studied. For example, 4(250) indicates that there were four randomized controlled trials with 250 enrolled patients. The 250 patients include all patients irrespectively of randomization to either treatment group with TA or control arm. Some trials have more than two arms, and therefore, simplification was necessary. The minimum requirement for these studies was randomization to a control arm and a test arm. The quality of the study is not reflected here. Example: Two randomized studies with 50 patients in each arm and one randomized study with 75 patients in each arm will be denoted as 3(350).

I   Controlled trials (CT): the notation is similar to randomized controlled trials. Studies listed here were not randomized. The control group could be historical or concurrent to the treatment group.

J   Case series (CS). Number of case series (with total number of patients reported). We required that the case series described at least three patients. Case series with two patients were included in case reports. Example: 4(56) implies that there were four case series with the total number of reported patients of 56.

K   Case report (CR). Number of case reports (with total number of patients reported)—this information was derived also from abstract case reports from ASFA, ASH, AABB Annual meetings and meetings of other organizations relevant to the discussed entity starting January 1, 2004. The committee decided that if the report has not been published in peer reviewed literature within five years it will not be included in the total number of case reports.If there are more than 50 case reports or there is a significant number of larger studies either >50 or NA (not applicable) was used, respectively.

L   The strength of evidence was assigned based on the grading system used by the University HealthCare Consortium as discussed in the text. If there were multiple TA modalities used the attempt was made to assign strength of evidence to each modality.

M   A brief description of the discussed entity is provided here. Typically, this entry contains information on clinical signs and symptoms, pathophysiology, typical presentation and the severity of the disease.

N   This section provides brief description of therapeutic modalities available to treat the disease. The committee attempted to cover all reasonable modalities (e.g., medications, surgical procedures, etc.); however, this section is not intended to provide extensive discussion of any treatment modality. In addition, for some entities the management of standard therapy failure is discussed (e.g., steroid), especially when the failure of established therapies may trigger the use of therapeutic apheresis.

O   This section discusses a rationale for therapeutic apheresis as well as supporting evidence of its use. Most important reports are briefly discussed here. The effort was made to discuss a rationale for TA in the context of the current understanding of pathophysiology.

P   This section briefly describes technical suggestions relevant to the treated disease, which the committee believed were important to improve quality of care or increase chances of positive clinical outcome. Not all diseases have specific technical notes; in such instances a general statement referring to the introductory text is provided.

Q   This section specifies commonly used volumes of plasma or blood treated. Typically this value for plasma exchange is between 1 and 1.5 total plasma volumes (TPV).

R   The proposed frequency of treatment is listed here. The frequency is based on the data from the published reports however, due to variability of such reports; the committee suggested what is believed to be the clinically most appropriate frequency. Application of this information is left to the treating physician.

S   The type of replacement fluid most frequently used is listed here. Terms such as plasma or albumin were used to denote the type of replacement fluid. No attempt was made to include all possible variations (e.g., 4% vs. 5% albumin; fresh frozen plasma vs. thawed plasma). In addition, blood component modifications are listed here, if relevant (e.g., RBC modifications for red cell exchange). 'None' is used when there is not replacement fluid necessary (i.e., extracorporeal photopheresis).

T   This section provides basic criteria for discontinuation of apheresis procedures (i.e., end points, outcomes both clinical and laboratory). In some instances a number of procedures/series, which could be reasonably used in the particular clinical situation, is suggested to evaluate efficacy of TA in the particular clinical situation. The committee believes that a thoughtful approach to the patient is required to establish reasonable and scientifically sound criteria for discontinuation of treatment. This section does not replace the need for conversation between treating physician and apheresis physician.

V   Due to limitation of the space only most germane references were used for each fact sheet. For interested readers additional information can be obtained after perusing the cited references. All references are combined and printed at the end of this article.

U   The terms used to identify most relevant articles are listed here.

Design of the Fact Sheet

With the support of the ASFA Board of Directors, the ASFA Clinical Categories Subcommittee made minimal changes in the design of the fact sheet from the Fourth Special Issue. The single most important modification is inclusion of the recommendation grade as described above. Also, the committee has decided to remove the field ''disease group,'' which has been found to be not only arbitrary but also recently more difficult to assign as the boundaries between specialties are less firm. The information, provided in the fact sheet format, is comprehensive but limited in length to facilitate its
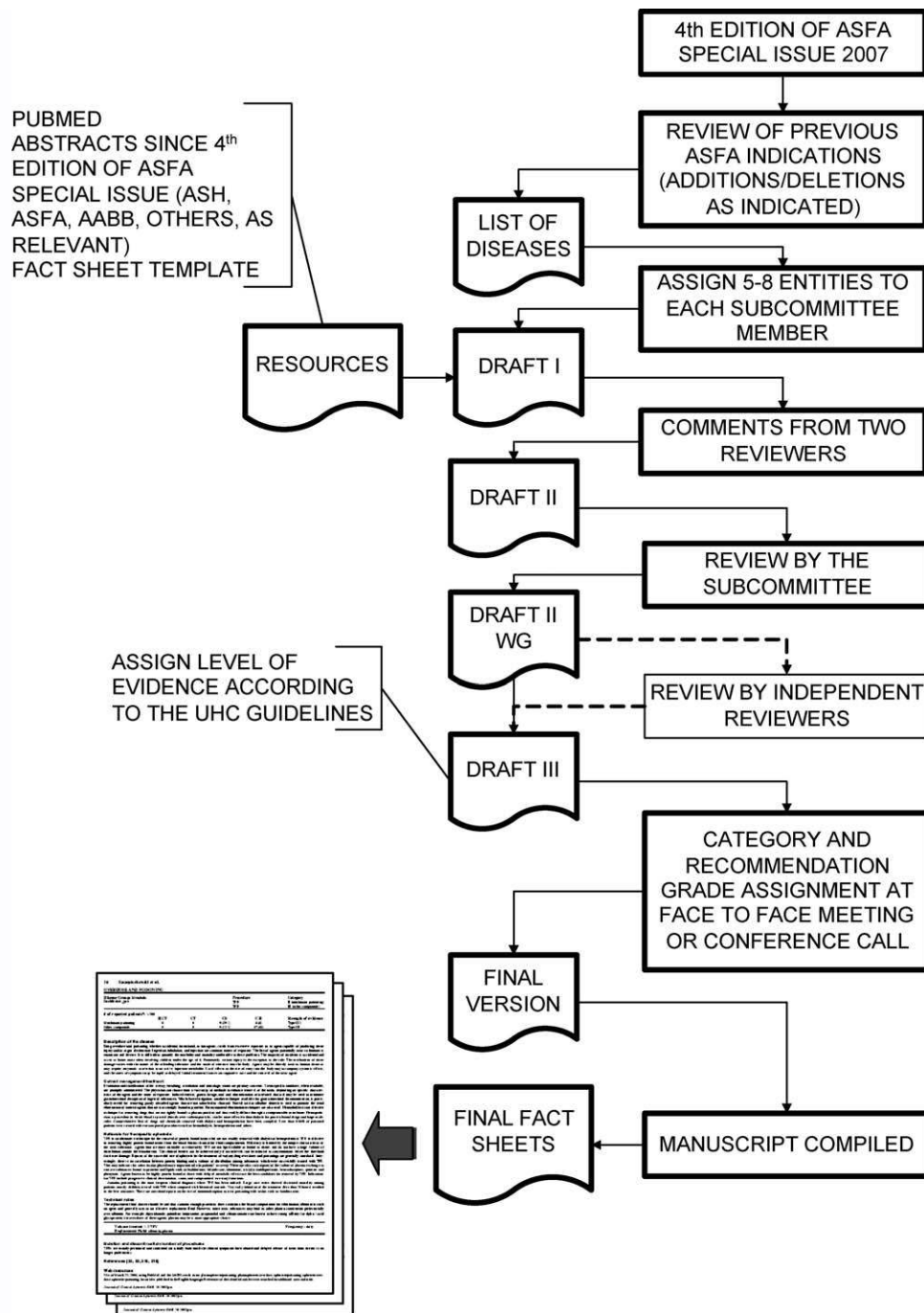
Fig. 2. Systematic approach to category assignment, grade recommendation and ASFA Fact Sheet generations and revisions used in the ASFA Special Issue 2010.

use as a quick reference. The design of the fact sheet and explanation of information contained is included in Figure 1. The authors encourage the reader to use this figure as a guide to interpretation of all entries in the fact sheets as substantial condensing of available information was required to achieve this user friendly format. The references provided are not meant to be exhaustive but rather serve as a starting point in a search for more information.

With very few exceptions the World Wide Web resources that were utilized by the committee members were excluded from the reference section and are available on the ASFA web site (www.apheresi-s.org). This decision was made to minimize the risk of sending a reader to resources, which may not be available any longer, while at the same time allowing the subcommittee to periodically review the content of the websites.

TABLE IV. Modified McLeod's Criteria for Evaluation of Efficacy of Therapeutic Apheresis [14]

Evidence	McLeod's criteria	Explanation
Mechanism	''Plausible Pathogenesis''	The current understanding of the disease process supports a clear rationale for the use of therapeutic apheresis modality.
Correction	''Better Blood''	The abnormality, which makes therapeutic apheresis plausible, can be meaningfully corrected by its use.
Clinical Effect	''Perkier Patients''	There is a strong evidence that therapeutic apheresis confers benefit that is clinically worthwhile, and not just statistically significant.

ASFA Category Assignments for 2010

A novel process for ASFA category assignment has been developed to facilitate accuracy and timely future updates for therapeutic apheresis indications. The committee-based approach is comprehensive and systematic in assembling objective evidence for disease indications, with emphasis on the quality of evidence and strength of recommendation [1].

A Clinical Categories Subcommittee consisting of 10 ASFA members was established in 2005. The process of category assignments was similar to the Fourth Special Issue. The group was asked to review, revise, and amend indications for therapeutic apheresis. The process of developing new indications consisted of four steps (Fig. 2). Step I created a list of diseases to be included. Step II assigned each of the working group members five to eight diseases to review. At a minimum, the review consisted of identifying all articles published in the English language, which described the use of therapeutic apheresis. In addition, for diseases with a small number of publications, all abstracts presented since the fourth edition of the Special Issue was published at ASFA, AABB, and ASH annual meetings were included in the analysis, as well as abstracts presented in the meetings of other professional organizations, when appropriate. Step III consisted of circulating the first draft of the submission to two other members of the subcommittee for editorial comments. On the basis of these comments the author created Draft II. In step IV, all fact sheets were finalized and each disease was assigned an ASFA category and grade of recommendation at a face-to-face meeting and conference calls of the subcommittee in fall and winter 2009. In addition, if the application of apheresis was for a specific disease presentation, then this was added to the categorization. The category assignment and recommendation grade were based upon the literature and determined by consensus of all subcommittee members. There was a thorough discussion with a final consensus or anonymous voting on the diseases without a clear category assignment. When the strength of evidence was considered, the members of the subcommittee were encouraged to use ''McLeod's Criteria,'' which are summarized in a modified form in Table IV [14]. We encourage the practitioners of apheresis medicine to use these criteria when considering the use of therapeutic apheresis in a medical condition, which is not categorized by ASFA. However, the recommendation grade added additional and likely critical dimension to evaluation of clinical benefit of the therapeutic apheresis in reviewed diseases. ASFA categories and grade of recommendation are summarized in Table V.

The introduction of revised definitions of ASFA categories and recommendation grades resulted in recategorization of several diseases. The reader may initially consider some changes as surprising. We decided to use babesiosis as an example to explain the thought process with new categories and recommendations. First, babesiosis was divided into severe and high risk populations in the Fifth Special Issue rather than just severe as it was done in the Fourth Special Issue [2]. The published literature now supports the use of RBC exchange in both populations. In addition, in patients with severe disease, RBC exchange would be first-line treatment along with antimicrobials, hence the ASFA category I was assigned. Although in patients, who are at high risk of developing severe disease, such as asplenic or immunocompromised patients, antimicrobials are used first and then if there is lack of adequate clinical response RBC exchange would be a second-line treatment, hence ASFA category II. The grade of recommendation is affected by the strength of evidence resulting in stronger recommendation for severe babesiosis (Grade 1B) and weakest possible recommendation for the use of RBC exchange in a high risk population (Grade 2C).

The relationship between the ASFA Categories and recommendation grades is illustrated in Figure 3. All categorized indications (i.e., Category I through IV) were analyzed after the committee completed its work. The assigned categories and their respective recommendation grades were plotted. The higher number of indications is caused by some diseases having several categories and recommendation grades. It can be easily appreciated that category III indications have the highest number of Grade 2B and Grade 2C recommendations (i.e., the weakest recommendations). Category IV indications are spread through the entire spectrum of recommendation grades (i.e., Grade 2C to Grade 1A), which can be expected as there is a variable level of evidence, which puts these diseases into this category. This figure illustrates ASFA categories being deeply immersed in evidence-based medicine.

TABLE V. ASFA 2010 Indication Categories for Therapeutic Apheresis

Disease name[a]	Special condition	TA modality	Category	Recommendation grade	Page
ABO incompatible hematopoietic stem cell transplantation	HPC, Marrow	TPE	II	1B	95
	HPC, Apheresis	TPE	II	2B	
ABO incompatible solid organ transplantation	Kidney	TPE	II	1B	96
	Heart (<40 months of age)	TPE	II	1C	
	Liver perioperative	TPE	III	2C	
Acute disseminated encephalomyelitis		TPE	II	2C	97
Acute inflammatory demyelinating polyneuropathy (Guillain-Barré Syndrome)		TPE	I	1A	98
Acute liver failure		TPE	III	2B	99
Age related macular degeneration	Dry AMD	Rheopheresis	III	2B	100
Amyloidosis, systemic		TPE	IV	2C	NA
Amyotrophic lateral sclerosis		TPE	IV	1B	NA
ANCA- associated rapidly progressive glomerulonephritis (Wegener's Granulomatosis)	Dialysis dependence	TPE	I	1A	101
	Diffuse alveolar hemorrhage (DAH)	TPE	I	1C	
	Dialysis independence	TPE	III	2C	
Anti-glomerular basement membrane disease (Goodpasture's syndrome)	Dialysis independence	TPE	I	1A	102
	Diffuse alveolar hemorrhage (DAH)	TPE	I	1B	
	Dialysis dependent and no DAH	TPE	IV	1A	
Aplastic anemia; pure red cell aplasia	Aplastic anemia	TPE	III	2C	103
	Pure red cell aplasia	TPE	II	2C	
Autoimmunic hemolytic anemia: warm autoimmune hemolytic anemia; cold agglutinin disease	Warm autoimmune hemolytic anemia	TPE	III	2C	104
	Cold agglutinin disease (life threatening)	TPE	II	2C	
Babesiosis	Severe	RBC exchange	I	1B	105
	High-risk population	RBC exchange	II	2C	
Burn shock resuscitation		TPE	IV	2B	106
Cardiac allograft rejection	Prophylaxis	ECP	I	1A	107
	Treatment of rejection	ECP	II	1B	
	Treatment of antibody mediated rejection	TPE	III	2C	
Catastrophic antiphospholipid syndrome		TPE	II	2C	108
Chronic focal encephalitis (Rasmussen's Encephalitis)		TPE	II	2C	109
		IA	II	2C	
Chronic inflammatory demyelinating polyradiculoneuropathy		TPE	I	1B	110
Coagulation factor inhibitors		IA	III	2B	111
		TPE	IV	2C	
Cryoglobulinemia	Severe/symptomatic	TPE	I	1B	112
	Secondary to Hepatitis C virus	IA	II	2B	
Cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome	Erythrodermic	ECP	I	1B	113
	Non-erythrodermic	ECP	III	2C	
Dermatomyositis or polymyositis		TPE	IV	1B	NA
		Leukocytapheresis	IV	1B	NA

TABLE V. ASFA 2010 Indication Categories for Therapeutic Apheresis (Continued)

Disease name[a]	Special condition	TA modality	Category	Recommendation grade	Page
Dilated cardiomyopathy	NYHA II-IV	IA	III	2B	114
	NYHA II-IV	TPE	III	2C	
Familial hypercholesterolemia	Homozygotes	Selective Removal	I	1A	115
	Heterozygotes	Selective Removal	II	1A	
	Homozygotes with small blood volume	TPE	II	1C	
Focal segmental glomerulosclerosis recurrent		TPE	I	1C	116
Graft-versus-host disease	Skin (chronic)	ECP	II	1B	117
	Skin (acute)	ECP	II	2C	
	Non-skin (acute/chronic)	ECP	III	2C	
Hereditary hemochromatosis		Erythrocytapheresis	III	2B	118
Hemolytic uremic syndrome	Atypical HUS due to complement factor gene mutations	TPE	II	2C	119
	Atypical HUS due to autoantibody to factor H	TPE	I	2C	
	Diarrhea associated HUS or typical HUS	TPE	IV	1C	
Hyperleukocytosis	Leukostasis	Leukocytapheresis	I	1B	120
	Prophylaxis	Leukocytapheresis	III	2C	
Hypertriglyceridemic pancreatitis		TPE	III	2C	121
Hyperviscosity in monoclonal gammopathies	Treatment of symptoms	TPE	I	1B	122
	Prophylaxis for rituximab	TPE	I	1C	
Immune thrombocytopenic purpura		TPE	IV	1C	NA
Immune complex rapidly progressive glomerulonephritis		TPE	III	2B	123
Inclusion body myositis		TPE	IV	2B	NA
		Leukocytapheresis	IV	2C	NA
Inflammatory bowel disease		Adsorptive cytapheresis	II	2B	124
Lambert-Eaton myasthenic syndrome		TPE	II	2C	125
Lung allograft rejection		ECP	II	1C	126
Malaria	Severe	RBC exchange	II	2B	127
Multiple sclerosis	Acute CNS inflammatory demyelinating disease unresponsive to steroids	TPE	II	1B	128
	Chronic progressive	TPE	III	2B	
Myasthenia gravis	Moderate-severe	TPE	I	1A	129
	Pre-thymectomy	TPE	I	1C	
Myeloma cast nephropathy	Cast nephropathy	TPE	II	2B	130
Nephrogenic systemic fibrosis		ECP	III	2C	131
		TPE	III	2C	
Neuromyelitis optica (Devic's syndrome)		TPE	II	1C	132
Overdose, venoms, and poisoning	Mushroom poisoning	TPE	II	2C	133
	Invenomation	TPE	III	2C	
	Monoclonal antibody with PML	TPE	III	2C	
	Other compounds	TPE	III	2C	
Paraneoplastic neurologic syndromes		TPE	III	2C	134
		IA	III	2C	
Paraproteinemic polyneuropathies	IgG/IgA	TPE	I	1B	135
	IgM	TPE	I	1C	
	Multiple myeloma	TPE	III	2C	
	IgG/IgA or IgM	IA	III	2C	

TABLE V. ASFA 2010 Indication Categories for Therapeutic Apheresis (Continued)

Disease name[a]	Special condition	TA modality	Category	Recommendation grade	Page
Pediatric autoimmune neuropsychiatric disorders associated with streptoccal infections and Sydenham's chorea	PANDAS (exacerbation)	TPE	I	1B	136
	Sydenham's chorea	TPE	I	1B	
Pemphigus vulgaris		TPE	IV	2B	137
		ECP	III	2C	
Phytanic acid storage disease (Refsum's disease)		TPE	II	2C	138
Polycythemia vera and erythrocytosis	Polycythemia vera	Erythrocytapheresis	III	2C	139
	Secondary erythrocytosis	Erythrocytapheresis	III	2B	
POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes)		TPE	IV	2B	NA
Post transfusion purpura		TPE	III	2C	140
Psoriasis		TPE	IV	1B	NA
Red cell alloimmunization in pregnancy	Before intrauterine transfusion availability	TPE	II	2C	141
Renal transplantation	Antibody mediated rejection	TPE	I	1B	142
	Desensitization, living donor, positive crossmatch due to donor specific HLA antibody	TPE	II	1B	
	High PRA; cadaveric donor	TPE	III	2C	
Rheumatoid arthritis, refractory		IA	II	2A	143
		TPE	IV	1B	
Schizophrenia		TPE	IV	1A	NA
Scleroderma (Progressive systemic sclerosis)		TPE	III	2C	144
		ECP	IV	1A	
Sepsis with multiorgan failure		TPE	III	2B	145
Sickle cell disease	Acute stroke	RBC exchange	I	1C	146
	Acute chest syndrome	RBC exchange	II	1C	
	Prophylaxis for primary or secondary stroke; prevention of transfusional iron overload	RBC exchange	II	1C	
	Multi-organ failure	RBC exchange	III	2C	
Stiff-person syndrome		TPE	IV	2C	NA
Systemic lupus erythematosus	Severe (e.g. cerebritis, diffuse alveolar hemorrhage)	TPE	II	2C	147
	Nephritis	TPE	IV	1B	
Thrombocytosis	Symptomatic	Thrombocytapheresis	II	2C	148
	Prophylactic or secondary	Thrombocytapheresis	III	2C	
Thrombotic microangiopathy: drug-associated	Ticlopidine/Clopidogrel	TPE	I	2B	149
	Cyclosporine/Tacrolimus	TPE	III	2C	
	Gemcitabine	TPE	IV	2C	
	Quinine	TPE	IV	2B	
Thrombotic microangiopathy: hematopoietic stem cell transplant-associated		TPE	III	1B	150
Thrombotic thrombocytopenic purpura		TPE	I	1A	151
Thyroid storm		TPE	III	2C	152
Wilson's disease, fulminant	Fulminant hepatic failure with hemolysis	TPE	I	1C	153

[a]Diseases with names in bold have fact sheets in this publication.

Abbreviations: AMD, Age related macular degeneration; CNS, Central nervous system; DAH, Diffuse alveolar hemorrhage; HLA, Human leukocyte antigen; HUS, Hemolytic uremic syndrome; NYHA, New York Heart Association; PANDAS, Pediatric autoimmune neuropsychiatric disorders associated with streptoccal infections; PRA, Panel reactive antibody; PML, Progressive multifocal leukoencephalopathy.
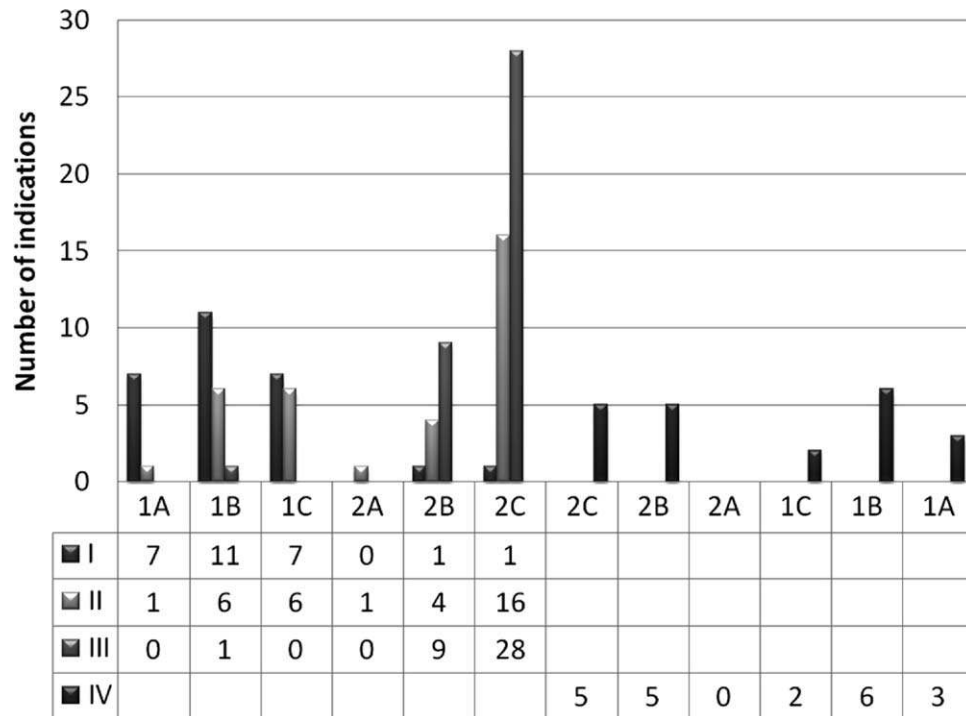
	1A	1B	1C	2A	2B	2C	2C	2B	2A	1C	1B	1A
■ I	7	11	7	0	1	1						
■ II	1	6	6	1	4	16						
■ III	0	1	0	0	9	28						
■ IV							5	5	0	2	6	3

Fig. 3.   The ASFA Category I–IV indications and the recommendation Grade in the ASFA Special Issue 2010.

TABLE VI. General Issues to be Considered When Evaluating a New Patient for Initiation of Therapeutic Apheresis

General	Description
Rationale*	Based on the established/presumptive diagnosis and history of present illness the discussion could include the rationale for the procedure, brief account of the results of published studies, and patient-specific risks from the procedure
Impact	The effect of therapeutic apheresis on comorbidities and medications (and vice versa) should be considered
Technical issues*	The technical aspects of therapeutic apheresis, such as a type of anticoagulant, a replacement solution, a vascular access, and a volume of whole blood processed (e.g., number of plasma volumes exchanged) should be addressed
Therapeutic plan*	Total number and/or frequency of therapeutic apheresis procedures should be addressed
Clinical and/or laboratory end-points*	The clinical and/or laboratory parameters should be established to monitor effectiveness of the treatment. The criteria for discontinuation of therapeutic apheresis should be discussed whenever appropriate
Timing and Location	The acceptable timing of initiation of therapeutic apheresis should be considered based on clinical considerations (e.g., medical emergency, urgent, routine etc.). The location where the therapeutic apheresis will take place should be also addressed (e.g., intensive care unit, medical word, operating room, outpatient setting). If the timing appropriate to the clinical condition and urgency level cannot be met, a transfer to a different facility should be considered based on the clinical status of the patient

Note: The above issues should be considered in addition to a routine note addressing patient's history, review of systems and physical examination.
*The ASFA Fact Sheet for each disease could be helpful in addressing these issues.

General Considerations

There are new textbooks in the field of apheresis medicine, which users of the Special Issue may find useful, including Apheresis: Principles and Practice, Third Edition [15]. The format of the Special Issue restricts the amount information, which can be provided in each fact sheet. In Table VI, we suggest information to be included in a consultation note before performing an apheresis procedure. This standard approach to consultation may be helpful to readers, who have less experience in this field. Also some of the issues related to specific diseases are clearly addressed in those disease specific fact sheets, particularly in the technical notes section.

An area of potential concern for the apheresis practitioner is the replacement fluid used during plasma exchange. If stated in the fact sheet that plasma exchange is performed daily, plasma may be indicated as part of replacement fluid to prevent severe coagulopathy from repetitive removal of coagulation factors through serial TPE. Additionally, maintaining the fibrinogen level >100 mg/dL is typically recommended to prevent increase risk of bleeding. In many instances, plasma supplement can be given toward the end of procedure.

Lastly, issues related to the timing of procedures, such as emergency (within hours), urgent (within a day), and routine, are not addressed directly in the fact sheets.

TABLE VII. Definitions of Various Apheresis Procedures

Procedure/term	Definition
Apheresis	A procedure in which blood of the patient or donor is passed through a medical device, which separates out one or more components of blood and returns remainder with or without extracorporeal treatment or replacement of the separated component
Extracorporeal photopheresis (ECP)	A therapeutic procedure in which buffy coat, separated from patient's blood, is treated extracorporeally with a photoactive compound (e.g., psoralens) and exposed to ultraviolet A light and subsequently reinfused to the patient during the same procedure
Erythrocytapheresis	A procedure in which blood of the patient or donor is passed through a medical device, which separates red blood cells from other components of blood, the red blood cells are removed and replaced with crystalloid or colloid solution, when necessary
Filtration selective removal	A procedure which uses a filter to remove components from the blood based upon size. Depending upon the pore size of the filters used, different components can be removed. Filtration based instruments can be used to perform plasma exchange or LDL apheresis. They can also be used to perform donor plasmapheresis where plasma is collected for transfusion or further manufacture
Immunoadsorption (IA)	A therapeutic procedure in which plasma of the patient, after separation from the blood, is passed through a medical device, which has a capacity to remove immunoglobulins by specifically binding them to the active component (e.g., Staphylococcal protein A) of the device
LDL Apheresis	The selective removal of low density lipoproteins from the blood with the return of the remaining components. A variety of instruments are available which remove LDL cholesterol based upon charge (dextran sulfate and polyacrylate), size (double-membrane filtration), precipitation at low pH (HELP), or immunoadsorption with anti-Apo B-100 antibodies
Leukocytapheresis (LCP)	A procedure in which blood of the patient or the donor is passed through a medical device, which separates out white blood cells (e.g., leukemic blasts or granulocytes), collects the selected cells and returns remainder of the patient's or the donor's blood with or without addition of replacement fluid, such as colloid and/or crystalloid solution. This procedure can be used therapeutically or in preparation of blood components
Plasma exchange (TPE)	A therapeutic procedure in which blood of the patient is passed through a medical device, which separates out plasma from other components of blood, the plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or combination of crystalloid/colloid solution
Plasmapheresis	A procedure in which blood of the patient or the donor is passed through a medical device, which separates out plasma from other components of blood and the plasma is removed (i.e. less than 15% of total plasma volume) without the use of replacement solution
Plateletapheresis	A procedure, in which blood of the donor is passed through a medical device, which separates out platelets, collects the platelets, and returns remainder of the donor's blood. This procedure is used in preparation of blood components (e.g., apheresis platelets)
RBC exchange	A therapeutic procedure in which blood of the patient is passed through a medical device, which separates red blood cells from other components of blood, the red blood cells are removed and replaced with donor red blood cells alone and colloid solution
Therapeutic apheresis (TA)	A therapeutic procedure in which a blood of the patient is passed through an extracorporeal medical device, which separates components of blood to treat a disease. This is a general term which includes all apheresis based procedures used therapeutically
Thrombocytapheresis	A therapeutic procedure, in which blood of the patient is passed through a medical device, which separates out platelets, removes the platelets and returns remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution

The importance of therapeutic apheresis in the treatment of a specific disease is addressed in detail. Because every patient is unique and there is a wide spectrum of presentation and progression for various diseases and conditions, the subcommittee felt that categorizing diseases and disorders in this way was not appropriate. The patient's clinical condition and situation should be considered when deciding the timing of treatment. This determination should be made through consultation between the requesting physician and the medical director of the apheresis unit using appropriate medical judgment. The subcommittee did feel that diseases that should be treated emergently, that is, in the middle of the night if warranted, are thrombocytopenic thrombotic purpura, acute chest syndrome in sickle cell disease, thrombocytosis, hyperleukocytosis, hyperviscosity, and malaria. These are life-threatening conditions where therapeutic apheresis is the primary mode of acute treatment.

GLOSSARY

Therapeutic apheresis procedures considered in this publication and included in the fact sheets are therapeutic plasma exchange (TPE), red blood cell exchange, erythrocytapheresis, thrombocytapheresis, leukocytapheresis, extracorporeal photopheresis (ECP), immunadsorption (IA), selective removal methods, adsorptive cytapheresis, and membrane differential filtration. We thought that it would be helpful to apheresis medicine community to agree on definitions of apheresis procedures. We attempted to summarize definitions of most commonly performed procedures in Table VII.

ABO INCOMPATIBLE HEMATOPOIETIC STEM CELL TRANSPLANTATION

Incidence: ABO incompatibility exists in about 20%-40% of HLA-matched allogeneic hematopoietic stem cell and bone marrow transplants	Procedure	Recommendation	Category
	TPE	Grade 1B [HPC(M)]	II
	TPE	Grade 2B [HPC(A)]	II

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
0	0	4 (465)	10 (21)	Type II-3

Terminology: HPC, Apheresis [HPC(A)]; HPC, Marrow [HPC(M)]; HPC, Cord Blood [HPC(CB)].

Description of the disease

Major incompatibility refers to the presence of natural antibodies in the recipient against the donor's A or/and B blood group antigens. These isoagglutinins may cause acute hemolysis of the red cells present in the transplanted stem cell product. Blood hematopoietic progenitor cell (HPC) products collected by apheresis (HPC, Apheresis) carry a lower risk of hemolysis due to reduced red cell contamination (2-8%) as compared to bone marrow HPC products, which contain 25-35% red cells. In the latter case, either the product needs to be red cell-reduced (easier to perform) or the patient's isoaglutinin titer needs to be lowered (to <32) to prevent an acute hemolytic reaction. Delayed erythrocyte engraftment occurs in 20% of patients after major ABO mismatched transplantation. Pure red cell aplasia (PRCA) occurs rarely due to persistence of anti-A that destroys donor erythroid precursors (e.g. with an O recipient and A donor). In minor incompatibility, the HPC donor product has antibodies against the recipient's A and/or B antigen. These products should be plasma-reduced if the titer is >256 when the plasma volume is >200 mL to prevent an acute hemolytic transfusion reaction. In addition, donor lymphocytes (passenger B cells) are capable of mounting an antibody response against the recipient's A or B antigens, which can result in severe and even fatal hemolysis (generally occurring 7-10 days post HPC infusion). Peripheral blood stem cell (PBSC) transplantation has greater risk of this complication than bone marrow transplantation, since HPC, Apheresis products have 16-fold more CD3+T lymphocytes and 11-fold more CD19+ B lymphocytes than HPC, Marrow products. T cell depletion and cyclosporine-A are risk factors for this complication, whereas methotrexate reduces this risk by suppressing the proliferation of donor lymphocytes.

Current management/treatment

In major incompatibility, red cell reduction of the HPC product can be performed to prevent acute hemolytic transfusion reaction. In minor incompatibility, plasma reduction may prevent the same complication. For delayed erythroid engraftment or PRCA post transplantation, various management strategies have been reported including high-dose erythropoietin, plasma exchange (TPE), immunoadsorption, rituximab, donor lymphocyte infusions, discontinuation of cyclosporine, and antithymocyte globulin. The optimal treatment is currently not well defined. Acute hemolysis due to passenger lymphocytes after minor ABO incompatible transplantation (mostly related to anti-A), is usually managed with aggressive transfusion or red blood cell exchange with O RBCs. HPC product derived from cord blood is contaminated with a large number of red cells but the A and B antigens are poorly developed in a newborn and thus there is no concern for hemolysis. Similarly, due to absence of high titer anti-A or anti-B isoagglutinins and mature lymphocytes in the product, there is no concern for hemolysis of recipient's incompatible red cells.

Rationale for therapeutic apheresis

With major ABO incompatibility, TPE can be used to reduce recipient anti-A and anti-B titers that could cause acute hemolysis and/or PRCA. Intervention to prevent acute hemolysis is generally recommended when an HPC product containing >20 mL of donor red cells is to be infused into a recipient with an isoagglutinin titer >16. However, the data about the correlation between pretransplant isoagglutinin titers and development of PRCA are inconclusive. If TPE is required because the HPC product cannot be red cell reduced, IgM isoagglutinin (predominantly intravascular) will be more effectively removed than IgG because IgG is almost equally distributed into both intra- and extra-vascular compartments. In a recent retrospective study of 153 ABO incompatible transplants, pretransplant reduction of isoagglutinin titers showed significant reduction of PRCA and delayed RBC engraftment as compared to non-reduction (p<0.001). Antibody titer reduction was accomplished by transfusion of ABO incompatible donor type RBCs, plasma exchange or combination of the two. In minor ABO incompatibility with passenger lymphocyte-induced acute hemolysis at 7-12 days after infusion (mostly anti-A), TPE can reduce antibody and ameliorate red cell destruction. Other option would be to replace the recipient's A red cells with O red cells by exchange transfusion.

Technical notes

TPE should be performed before infusion of major ABO incompatible HPC product, using albumin or combination of albumin and plasma compatible with both donor and recipient as replacement fluid.

Volume treated: 1 to 2 TPV	**Frequency:** daily
Replacement fluid: albumin; plasma	

Duration and discontinuation/number of procedures

The goal should be to reduce the IgM or IgG antibody titers to ≤16 immediately before HPC transplantation. If there is a delayed red cell recovery or PRCA, TPE may be performed. See fact sheet on PRCA for more information

References [17–23]

*As of November 1, 2009 using PubMed and the MeSH search terms ABO incompatible stem cell and bone marrow transplantation, plasmapheresis, plasma exchange, pure red cell aplasia for articles published in the English language. References of the identified articles were searched for additional cases and trials.

ABO INCOMPATIBLE SOLID ORGAN TRANSPLANTATION

Incidence: rare		Procedure	Recommendation	Category
		TPE	Grade 1B	II (kidney)
		TPE	Grade 1C	II (heart <40 months of age),
		TPE	Grade 2C	III (liver perioperative)

# of reported patients*: >300					
	RCT	CT	CS	CR	Strength of evidence
Kidney	0	0	21 (755)	28 (45)	Type II-3
Heart	0	0	2 (31)	1 (1)	Type II-3
Liver	0	0	6 (54)	8 (8)	Type II-3

Description of the disease

In 2009, 100,000 patients were on waiting lists to receive organ transplants. Only 24,000 underwent transplant of which approximately 40% received organs from a living donor. Due to a shortage of compatible organs for transplantation, ABO incompatible (ABOi) living donors are increasingly used. Major incompatibility refers to the presence of natural antibodies in the recipient against the donor's A or/and B blood group antigen. These antibodies may cause hyperacute/acute humoral rejection of the organ due to endothelial damage because A and B antigens are expressed on the vascular endothelium. ABOi exists in approximately 35% donor-recipient pairs by virtue of ABO blood group distribution in general population. The A2 blood group has reduced expression of A antigen on their RBCs and endothelium and, therefore, group A2 donors are preferred over group A1 donor for group O or B recipients in kidney transplantation with very low risk for graft rejection. In liver transplantation, there is not sufficient evidence regarding better graft survival in group A2 versus group A1 donors in ABO incompatible transplants. Generally, ABO identical transplantations are performed in liver transplantation; however, in emergent situations, ABOi transplants are occasionally performed. In this situation, TPE may be performed to prevent hyperacute rejection by removal of the preformed anti-A and/or anti-B antibodies. ABOi heart transplantation should be avoided if possible because of the risk of hyperacute rejection even though there is less ABO antigen expression in the heart compared to other tissues. When this has been performed, there is a high incidence of early graft failure in adults. In infants and young children (up to 40 months of age), ABOi heart transplantation results are much better as these patients have very low anti-A or anti-B titers (<4) due to a relatively immature immune system. Recently published case reports have used rituximab in ABOi transplantation, both prophylactically and to treat rejection. Minor incompatibility occurs where the organ donor has naturally occurring ABO antibodies against the recipient. Donor lymphocytes present within the graft (known as passenger lymphocytes) may produce antibodies against recipient RBCs resulting in severe hemolysis.

Current management/treatment

Most published reports on ABOi solid organ transplantations involve removal of anti-A or anti-B antibodies in conjunction with immunosuppressive treatment with drugs such as tacrolimus and mycophenolate mofetil; and monoclonal antibodies, daclizumab and rituximab. Rituximab is effective in B cell ablation but does not affect plasma cells. Other immunotherapy modalities including intravenous immunoglobulins (IVIG) and antithymocyte globulins (ATG) have important roles in the transplant process. Splenectomy, while formerly considered an absolute requirement for ABOi renal transplants, has recently been used only to treat refractory rejection in renal transplantation. Eculizumab (monoclonal anti-C5 antibody) may also have a role in treatment of rejection.

Rationale for therapeutic apheresis

There are no controlled clinical trials using TPE in ABOi solid organ transplantations. Due to past experiences of hyperacute and acute rejection of ABOi solid organs, TPE has been used as an adjunct therapy to reduce anti-A or anti-B antibody titers in the peri-transplant period, thus preventing hyperacute/acute rejection and improving graft survival. Retrospective review of organ survival data on ABO incompatible patients treated with TPE compares well with ABO compatible transplants. Therefore, TPE has been included in preparatory regimens for ABOi solid organ transplantation as an adjunct with different immunosuppression therapies and IVIG. In ABOi kidney transplantation, TPE is part of a preconditioning protocol to lower antibody titer to <4 prior to the transplant procedure. For ABOi heart transplantation, titer has been reduced to <4 in children (age up to 40 months) with 80-100% survival. In case series for ABOi liver transplantations, the anti-A or anti-B titers are reduced to <16 in Japanese and US studies and <8 in Italian studies. Graft survival in these ranges from 45-100%. In an Italian ABOi liver transplant study, TPE along with IVIG plus extracorporeal photopheresis was superior (87%) to TPE alone (45%) for graft survival at 18 months. It is difficult to compare the effectiveness of TPE for ABOi solid organ transplantation in different studies due to the fact that immunosuppressive and/or immunomodulatory regimes used are different. Apart from TPE, specific A or B antigen immunoadsorption columns have been used in Europe to selectively remove anti-A or anti-B antibodies.

Technical notes

The replacement fluid for TPE is 5% albumin with or without FFP (compatible with both the recipient and donor), depending upon presence or absence of coagulopathy. Thus, in liver transplantation TPE can be performed with 100% FFP for moderate to severe coagulopathy or 50% albumin and 50% FFP for antibody removal with mild coagulopathy. For heart and kidney cases 5% albumin is generally used as the replacement fluid.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily, or every other day
Replacement fluid: albumin; plasma	

Duration and discontinuation/number of procedures

The goal should be to reduce the antibody titer (IgM and IgG) to ≤8 in liver transplantation and ≤4 in renal transplantation. This titer can be achieved usually in 2-5 days, depending upon the baseline titers. The antibody titers may increase 3-7 days after transplantation; therefore, daily antibody titer for the first 2 weeks post-transplantation is necessary. During the following 2 weeks, antibody titer measurement every second day helps to prevent immunologic graft events. If the antibody titer is high with or without humoral rejection, TPE should be performed again in the post-transplantation period (Liver transplant data are available only for the first 2 weeks). In renal transplantation, usually three more TPEs are performed postoperatively (every second or third day followed by IVIG). If the antibody titer can be maintained at <8 in post transplant first week and 16 in second week, the risk of humoral rejection is decreased.

References [17,24–35]

*As of November 3, 2009 using PubMed and the MeSH search terms ABO incompatible, liver, heart and kidney transplantation, plasma exchange and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Incidence: ~0.8 per 100,000/year in the US				**Procedure**	**Recommendation**	**Category**
				TPE	Grade 2C	II

# of reported patients*: <100					
RCT	**CT**	**CS**	**CR**	**Type of evidence**	
0	0	4 (23)	15 (20)	Type III	

Description of the disease

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory monophasic demyelinating disease that predominantly affects the white matter of the brain and spinal cord, which typically occurs after a viral or bacterial infection or vaccination. The pathogenesis is thought to be disseminated multifocal inflammation and patchy demyelination associated with transient autoimmune response against myelin or other autoantigens. Viral or bacterial epitopes resembling myelin antigens have the capacity to activate myelin reactive T cell clones through molecular mimicry, and thus can elicit a CNS-specific autoimmune response. Alternatively, the viral or bacterial superantigens could activate existing myelin autoreactive T cells clones through a nonspecific inflammatory process. ADEM typically begins within days to weeks following the antigenic challenge. The typical presentation is that of an acute encephalopathy (change in mental status) accompanied by multifocal neurological deficits (ataxia, weakness, dysarthria, and dysphagia). It is usually a monophasic illness that lasts from 2 to 4 weeks. However, recurrent or multiphasic forms have been reported. Children and young adults are predominantly affected. The mortality rate is around 5%, with complete recovery in 50%-75% of cases.

MRI is the diagnostic imaging modality of choice for the demyelinating lesions of ADEM. Characteristic lesions seen on MRI appear as patchy areas of increased signal intensity with typical involvement of deep cerebral hemispheric and subcortical white matter, as well as lesions in the basal ganglia, gray-white junction, brain stem, cerebellum and spinal cord. The differentiation of ADEM from a first attack of multiple sclerosis (MS) has prognostic and therapeutic implications. ADEM has these features which help to distinguish it from MS: florid polysymptomatic presentation, lack of oligoclonal band in CSF, predominance MRI lesions in the subcortical region with relative sparing of the periventricular area and complete or partial resolution of MRI lesions during convalescence. New lesions should not appear unless a clinical relapse has occurred.

Current management/treatment

Once ADEM is diagnosed, the therapeutic aim is to abbreviate the CNS inflammatory reaction as quickly as possible, and to speed up clinical recovery. There is no standard therapy for ADEM, and treatments are based on the analogy of the pathogenesis of ADEM with that of MS. High-dose intravenous corticosteroids, such as methylprednisolone, at a dosage standard for MS relapses have been commonly used, followed by a prolonged oral prednisolone taper of 3-6 weeks. Corticosteroids are considered effective because of their anti-inflammatory and immunomodulatory effects with additional beneficial effect on cerebral edema. Corticosteroids hasten recovery and result in clinical improvement in up to 60% of patients. TPE should be considered for patients with severe ADEM, who respond poorly to steroid treatment or in whom it is contraindicated. Additionally, IVIG is also used and is reserved for patients who do not respond to corticosteroids.

Rationale for therapeutic apheresis

TPE is used and has a clearly defined role in other neurological conditions that are presumed to be immunologically mediated. TPE works by removing presumed offending autoantibodies as well as through immunomodulation. In the acute phase of ADEM, cytokines such as tumor necrosis factor, soluble tumor necrosis factor receptor 1, IL-6 and IL-10 are elevated. Antibodies to gangliosides, such as GM1 and CD1a, and myelin basic protein-reactive T-helper 2 cells, may be present, which can be removed by TPE.

Technical notes

See the introduction to this article.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

There is no clear standard based upon which to make recommendations as to the optimum use of TPE in ADEM. In the largest case study, TPE achieved moderate and marked sustained improvement in 50% of the patients. Factors associated with improvement include male sex, preserved reflexes and early initiation of treatment. In most published literature, response was noticeable within days, usually after 2-3 exchanges. If improvement is not observed early in treatment, then it is unlikely a response will occur. TPE therapy consists of 3-6 treatments, most commonly 5.

References: [36–47]

*As of September 14, 2009 using PubMed and the MeSH search terms Acute Disseminated Encephalomyelitis, plasmapheresis, therapeutic plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

ACUTE INFLAMMATORY DEMYELINATING POLYNEUROPATHY (GUILLAIN-BARRÉ SYNDROME)

Incidence: 1-2 per 100,000/year				**Procedure** TPE	**Recommendation** Grade 1A	**Category** I

# of reported patients*: >300					
RCT	**CT**	**CS**	**CR**	**Type of evidence**	
19 (1770)	0	9 (369)	10 (11)	Type I	

Description of the disease

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) or the Guillain-Barré Syndrome is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. Typically the disease begins with symmetrical muscle weakness and paresthesias that spread proximally. Progression, which can occur briskly over several weeks, may involve respiratory and oropharyngeal muscles in more severe cases. Thus, mechanical ventilation is required for approximately 25% of patients. Autonomic dysfunction can cause variability in blood pressure and heart rate. Spontaneous recovery may occur, however up to 75% of patients develop long-term neurologic deficits. Mortality is estimated at 5%. The Miller-Fisher variant is characterized by opthalmoplegia, ataxia, and areflexia. AIDP is distinguished from Chronic Inflammatory Demyelinating Polyradiculoneuropathy which is a chronic disorder (see separate fact sheet). An autoimmune pathogenesis is strongly suggested due to the presence of antibodies to the myelin sheath constituents in the majority of patients as well as in animal models of the disease. Observations of preceding infectious illness, such as Campylobacter infection, suggest cross-reactive antibodies may be a component in disease pathogenesis.

Current management/treatment

Since spontaneous recovery is anticipated in most patients, supportive care is the mainstay of treatment in ambulatory patients with AIDP. Severely affected patients may require intensive care, mechanical ventilation, and assistance through the paralysis and necessary rehabilitation over several months to a year or more. Corticosteroids have not been shown helpful when used alone. TPE was the first therapeutic modality to impact the disease favorably and several major randomized controlled clinical trials have confirmed its efficacy. An international randomized trial compared TPE, IVIG and TPE followed by IVIG in 383 adult patients with severe AIDP and found all three modalities to be equivalent. There were no differences in the three treatment groups in mean disability improvement at 4 weeks nor the time to be able to walk without assistance (TPE group 49 days, IVIG group 51 days and TPE/IVIG group 40 days). Other therapeutic modalities studied include immunoadsorption apheresis, CSF filtration, and double filtration plasmapheresis. Since IVIG is readily available, it is frequently used as initial therapy; the typical dose is 0.4 g/kg for 5 consecutive days.

Rationale for therapeutic apheresis

The favored etiology of AIDP is autoimmune antibody-mediated damage to the peripheral nerve myelin. The results of several controlled trials comparing TPE to supportive care alone indicate TPE treatment can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones. While recovery with TPE is improved, the duration of disability from AIDP remains significant. For example in the French Cooperative Study, median time to wean from mechanical ventilation was 18 days versus 31 days for TPE compared to control, respectively. In the North American Trial the median time to walk without assistance was 53 days versus 85 days. Of note, the Cochrane Neuromuscular Disease Group review of TPE in AIDP found that TPE is most effective when initiated within 7 days of disease onset.

Technical notes

The typical TPE strategy is to exchange 200-250 mL of patient plasma per kg body weight over 10-14 days. This will generally require 5-6 TPE procedures with 5% albumin replacement. Fresh frozen plasma is not routinely used for replacement. Since autonomic dysfunction may be present, affected patients may be more susceptible to volume shifts, blood pressure and heart rate changes during extracorporeal treatment. Relapses may occur in approximately 10% of patients 2-3 weeks following either treatment with TPE or IVIG. When relapses occur, additional therapy, usually TPE, can be helpful. In AIDP patients with axonal involvement, TPE has been reported to be of greater potential benefit than IVIG.

Volume treated: 1 to 1.5 TPV **Replacement fluid:** albumin	**Frequency:** every other day

Duration and discontinuation/number of procedures

Five to six TPE over 10-14 days are recommended, see technical notes above for details.

References [43,48–67]

*As of December 31, 2009 using PubMed and the MeSH search terms acute inflammatory demyelinating poly radiculoneuropathy or Guillain Barré and plasmapheresis, plasma exchange, or apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

ACUTE LIVER FAILURE

Incidence: Exact incidence unknown. Liver transplantation rate is 5,000-6,000/ year in the US				Procedure	Recommendation	Category
				TPE	Grade 2B	III

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
0	0	36 (689)	50 (68)	Type II-3

Description of the disease

Acute liver failure (ALF) can develop in a normal liver (known as fulminant hepatic failure; FHF) or in chronic liver disease. The most common cause of ALF is viral hepatitis in the United States, and acetaminophen toxicity in the Great Britain. Other causes include drugs, ingestion of hepatotoxins, autoimmune hepatitis and Wilson's disease (see factsheet on Wilson's disease). The mortality rate in FHF is 50-90% due to acute metabolic disturbances, hepatic encephalopathy and severe coagulopathy; however, following liver transplantation, survival rate is >60%. Spontaneous recovery from FHF depends on the cause: high recovery rates are observed in fatty liver of pregnancy, acetaminophen ingestion and hepatitis A; hepatitis B has intermediate prognosis; other drugs and unknown etiologies have less than 20% recovery rate; and patients with FHF due to Wilson's disease rarely recover spontaneously. Without spontaneous recovery, the standard treatment of ALF is supportive care as a bridge to liver transplantation. Transplantation is performed for acute or chronic liver failure due to a variety of causes. About 30% of liver transplantation recipients have ALF. Generally ABO identical transplantations are performed except in emergent situations (see ABO incompatible solid organ transplantation).

Current management/treatment

Currently there are no FDA approved cell based liver support systems available in the United States and these therapies are still considered experimental. Some of these therapies include: Bioartificial liver (BAL), Extracorporeal Whole Liver Perfusion (ECLP) and Extracorporeal Liver Assist Device (ELAD). The non cell based therapies include: therapeutic plasma exchange, albumin dialysis, MARS (Molecular Adsorbents Recirculation System) and SPAD (Single Pass Albumin Dialysis). The supportive therapies consist of blood pressure support, prophylactic antibiotics, regulation of blood glucose, prevention of gastroduodenal hemorrhage, treatment of coma, correction of coagulopathy with FFP, prothrombin complex concentrate, recombinant factor VIIa and cryoprecipitate and conventional continuous veno-venous hemofiltration.

Rationale for therapeutic apheresis

In FHF, TPE can remove albumin bound as well as large molecular weight toxins, including aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phenols and other factors which may be responsible for hepatic coma, hyperkinetic syndrome, decreased systemic vascular resistance and cerebral blood flow. Most studies show improved cerebral blood flow, mean arterial pressure, cerebral perfusion pressure and cerebral metabolic rate, increased hepatic blood flow, improvements in other laboratory parameters such as cholinesterase activity or galactose elimination capacity. TPE also restores hemostasis by supplying the coagulation factors and removing activated clotting factors, tissue plasminogen activator, fibrin and fibrinogen degradation products. In some patients, the liver may regenerate during TPE and in other patients TPE can bridge to liver transplantation. In intractable pruritus, TPE is thought to remove the bile acids.

Technical notes

Since plasma has citrate as an anticoagulant and there is practically no functional liver, ACD-A ratio should be adjusted accordingly to prevent severe hypocalcemia in FHF. Simultaneous calcium infusion can be used if necessary. There is a preference for plasma as a replacement fluid due to moderate to severe coagulopathy; however, addition of albumin is acceptable. TPE will lower laboratory values such as bilirubin and hepatic enzymes due to removal and correct coagulation parameters due to supplementation, but do not necessarily reflect a change in the patient's clinical status. The rate of increase in these values after TPE needs to be followed.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily
Replacement fluid: plasma; plasma/albumin	

Duration and discontinuation/number of procedures

In FHF, daily TPE is performed until transplantation or self-regeneration occurs. The response to TPE should be evaluated in following morning's laboratory levels. Rarely TPE can be performed 2-3 times per week for 4 weeks in primary biliary cirrhosis to alleviate pruritus until a clinical response is observed; thereafter it can be continued at one to two week intervals or 1-2 times weekly for 2-6 weeks in BRIC (Benign recurrent intrahepatic cholestasis).

References [28,68–77]

*As of November 4, 2009 using PubMed and the MeSH search terms acute hepatic failure, fulminant liver failure and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

AGE RELATED MACULAR DEGENERATION

Incidence: 1.8 per 100,000/year		**Procedure**	**Recommendation**	**Category**
		Rheopheresis	Grade 2B	III (dry AMD)

# of reported patients*: >300

RCT	**CT**	**CS**	**CR**	**Type of evidence**
4 (263)	0	8 (101)	1 (1)	Type I

Description of the disease

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the Western world in those over 60 years of age. It affects the macula and is a progressive condition with loss of central vision. This affects the ability of the patient to read, recognize faces, and drive. AMD is characterized by the collection of debris (drusen) beneath the retinal pigment epithelium. This initial stage is called ''dry AMD.'' Over 10 years, 12.5% of those with the dry form will progress to ''wet AMD.'' This is characterized by the growth of blood vessels into the choroid (choroidial neovascularization). Risk factors for AMD include smoking, hypertension, elevated body mass index, as well as a direct correlation with cholesterol, fibrinogen, and α2-macroglobulin levels.

The pathogenesis of AMD has not been completely elucidated. With age, lipids are deposited within the sclera which becomes increasingly rigid. This compromises blood flow in the choroidal layer of the eye diminishing nutrient and oxygen supply to the retinal pigmented epithelium (RPE). The resulting hypoxia leads to a loss of the ability of the RPE to phagocytize cellular debris generated by normal turnover. This leads to deposition of extracellular debris (drusen) and dry AMD. These deposits lead to an increase of the distance that oxygen must diffuse leading to more hypoxia and greater RPE dysfunction. Increasing hypoxia eventually leads to RPE production of vascular growth factors resulting in the in-growth of blood vessels (choroidal neovascularization) and wet AMD.

Current management/treatment

The current treatment for dry AMD is limited and consists of high dose supplementation of vitamins C and E, beta carotene, and zinc. Wet AMD is treated by ablating the choroidial neovascularization with laser photocoagulation, transpupillary thermotherapy, photodynamic therapy, external beam irradiation, surgical removal of the neovascular membrane, or macular rotation.

Rationale for therapeutic apheresis

The rationale behind the use of Rheopheresis (also called double filtration plasmapheresis, cascade filtration plasmapheresis, or double membrane plasmapheresis) is that high-molecular weight molecules that have been associated with risk of AMD development (e.g., fibrinogen, LDL-cholesterol, fibronectin, von Willebrand factor) are removed from the patient's plasma. This results in a reduction in blood and plasma viscosity, platelet and red cell aggregation, and enhanced red cell membrane flexibility. This improves RPE perfusion, decreasing hypoxia, and allowing improved RPE function.

Numerous case series and four completed randomized controlled trials have reported efficacy of membrane differential filtration in treating AMD. These studies have shown improvement in the number of lines that can be read on ETDRS charts, improvement in the Pepper Visual Skills for reading test, decrease in a number of viscosity parameters, shortening of arteriovenous passage time, and improvement on electroretinogram. These studies have shown improvement shortly after completion of treatment which has lasted up to four years following the course of therapy. The Utah trial randomized 30 patients to three arms (treatment, placebo, and no treatment) and demonstrated improvement in the Pepper Visual Skills for reading test scores of +27% for the treatment arm but declines of -18 and -20% for the other arms. The MAC trial randomized 40 patients to treatment versus no treatment. Visual acuity in the treatment group improved by 0.63 lines on the EDTRS chart while the control decreased by 0.94 lines. The results of the MIRA-1 trial, a large randomized double-blinded placebo (sham procedure) controlled trial that enrolled 216 patients, failed to demonstrate a significant difference between controls and treatment groups due to the controls doing better than predicted. Analysis revealed that 37% of treated patients and 29% of control patients were protocol violators who did not fulfill the trial's inclusion criteria. Excluding protocol violators, who had vision loss due to other causes, demonstrated a significant improvement with treatment but the trial was under-powered. The most recent trial, Dry AMD Treatment with Rheopheresis Trial (ART), randomized 43 patients to treatment or no treatment in a 1 to 1 ratio. ART demonstrated an increase in best corrected visual acuity of 0.95 visual acuity lines on ETDRS charts in the treated group compared to the controls. Nine percent of treated patients demonstrated an increase in 2 or more visual acuity lines and none demonstrated a worsening of vision. No control patients demonstrated an improvement of 2 or more lines while 24% demonstrated visual acuity loss.

Technical notes

The majority of series and trials have been performed using double filtration plasmapheresis (DFPP). In this technique, plasma is separated from whole blood by filtration and then passed through a second filter. Low-molecular weight substances such as albumin pass through the filter while high-molecular weight substances are removed. One case series did indicate that TPE with albumin replacement was used to treat AMD but the trial included the use of other treatment modalities (e.g., tryptophan polyvinyl alcohol columns and DFPP) and the authors provide inadequate information to determine whether there was a benefit with TPE.

Studies have suggested that those with elevations in high-molecular weight plasma components have a better response and that patients with dry AMD respond better than those with wet AMD.

Volume treated: 0.8 to 1.2 TPV	**Frequency:** 8 to 10 treatments (two per week) over 8 to 21 weeks
Replacement fluid: NA	

Duration and discontinuation/number of procedures

Treatments performed as part of clinical trials have been per protocol. Efficacy has been reported to last for up to 4 years. One case series has suggested that after 12 months, two to four booster treatments could be considered depending upon the patient's course.

References: [78–92]

*As of February 12, 2010 using PubMed and the MeSH search terms macular degeneration and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials. This fact sheet includes abstracts in the summary of published reports and considers them in determining the recommendation grade and category.

ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (WEGENER'S GRANULOMATOSIS)

Incidence: 0.85 per 100,000/year	Procedure	Recommendation	Category
	TPE	Grade 1A	I (dialysis dependence)**
	TPE	Grade 1C	I [diffuse alveolar hemorrhage (DAH)]
	TPE	Grade 2C	III (dialysis independence)**

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
8 (296)	1 (26)	22 (347)	NA	Type I

**at presentation.

Description of the disease

ANCA-associated rapidly progressive glomerulonephritis is one cause of the clinicopathologic entity, rapidly progressive glomerulonephritis (RPGN). RPGN consists of rapid loss of renal function with the histologic finding of crescent formation in over 50% of glomeruli. These crescents represent a proliferation of cells within Bowman's space of the glomerulus due to the extravasation of proteins into this space. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes.

RPGN is NOT A SINGLE DISEASE ENTITY but is a clinical syndrome that can result from a number of etiologies. RPGN is divided into three categories based on the immunoflourescence pattern on renal biopsy. These categories are:

1) Linear deposits of IgG due to autoantibodies to type IV collagen representing anti-glomerular basement membrane GN (anti-GBM). It accounts for 15% of cases. (See fact sheet on anti-glomerular basement antibody disease).
2) Granular deposits of immune complexes caused by a variety of GNs including post-streptococcal GN, Henoch-Schönlein purpura, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis. Immune-complex RPGN accounts for 24% of cases of RPGN. (See fact sheet on immune-complex RPGN).
3) Minimal immune deposits in the glomerulus with the presence of anti-neutrophil antibodies (either C-ANCA or P-ANCA) in the serum. This pauci-immune RPGN, also referred to as ANCA-associated RPGN, is seen in Wegener's granulomatosis (WG) and microscopic polyangiitis (MP) and accounts for 60% of RPGN cases.

It is important for apheresis medicine practitioners to identify the specific category of RPGN present in their patient as TPE treatment protocols and responses differ among the three categories. In this special issue, anti-GBM and immune complex glomerulonephritis, the other major causes of RPGN, are discussed in separate fact sheets.

This fact sheet discusses ONLY ANCA-associated rapidly progressive glomerulonephritis. Pauci-immune GN is characterized by minimal immune deposits in the glomeruli and the presence of anti-neutrophil cytoplasmic antibodies (P-ANCA, C-ANCA in the serum). ANCA associated small vessel vasculitis encompasses a clinical spectrum of disease which ranges from renal-limited vasculitis to systemic involvement, including microscopic polyangiitis (MP), Wegener's granulomatosis, and the Churg-Strauss syndrome. The presentation of the pulmonary-renal syndrome associated with ANCA is clinically similar to anti-glomerular basement membrane disease (Goodpasture's Syndrome). When ANCA and anti-glomerular basement membrane antibody are both present, the disease should be considered to represent anti-GBM disease. See the fact sheet on anti-glomerular basement antibody disease. Diffuse alveolar hemorrhage (DAH) associated with ANCA vasculitis poses significant risk of mortality.

Current management/treatment

The current standard approach to management of ANCA small vessel vasculitis is combination therapy consisting of high-dose corticosteroids and cytotoxic immunosuppressive drugs. TPE has been added in life-threatening cases, such as ANCA with DAH, and also in patients who are dialysis dependent (or for whom initiation of dialysis is imminent). Other drugs that have been used include leflunomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors (mycophenolate mofetil, cyclosporin) and antibodies against T-cells. The European League Against Rheumatism (EULAR) recommends TPE as an adjunct for selected patients with rapidly progressive severe small and medium vessel vasculitis of the kidney.

Rationale for therapeutic apheresis

The presence of ANCA autoantibodies indicates a humoral component to disease pathogenesis and has fueled interest in TPE for management. Much of the published experience with TPE includes all forms of RPGN, not just exclusively Wegener's disease or ANCA-associated RPGN, which complicates interpretation of results. Six trials have examined the role of TPE in pauci-immune and immune-complex GNs. Of these 3 consisting of a total 87 patients, found no benefit of TPE over standard therapy. Two trials consisting of 62 patients found benefit in patients who were dialysis dependent at presentation but not those mildly affected. One trial consisting of 14 patients found benefit in all. These trials suggest that TPE is most beneficial in patients with dialysis dependency (at presentation) and offers no benefit over immunosuppression in milder disease. A controlled trial of ANCA associated RPGN of 26 patients suggests TPE may improve prognosis even in non-dialysis dependent patients. A retrospective case series reported effective management of pulmonary hemorrhage in ANCA vasculitis. In a European prospective study of 100 patients presenting with an initial diagnosis of ANCA-associated vasculitis with severe renal involvement, patients received standard therapy of oral corticosteroids and cyclophosphamide and were randomly assigned adjunctive therapy of either TPE or pulse methylprednisolone (1000 mg/d × 3 days). Randomization to the treatment arm which included plasma exchange (7 treatments over 14 days) was predictive of dialysis independence at 12 months (54% compared to 29%). Inclusion in this study required serum Cr >500 μmole/L (>5.7 mg/dL), intention to initiate dialysis within 48 hours, ANCA positivity, and histologic confirmation to exclude other causes of glomerulopathy. A Japanese national survey of MPO-ANCA patients treated with apheresis, however, did not demonstrate efficacy of apheresis in their patient population. A more recent randomized controlled trial (RCT) showed a significant improvement in renal recovery for ANCA patients presenting with Cr >5.8 mg/dL who received TPE compared to pulse methylprednisolone. A multicenter international RCT is in progress to establish the efficacy of TPE in additional to immunosuppressive therapy and glucocorticoids at reducing death and end-stage renal disease in ANCA positive vasculitis. (PEXIVAS; ClinicalTrials.gov registration number NCT00987389).

Technical notes

In patients with pulmonary hemorrhage, replacement with plasma is recommended to avoid dilutional coagulopathy resulting from non-plasma replacement.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin; plasma when DAH present	

Duration and discontinuation/number of procedures

Consider daily procedures in fulminant cases or with pulmonary hemorrhage then continuing every 2-3 days for total of 6-9 procedures.

References [93–117]

*As of December 31, 2009 using PubMed and the MeSH search terms ANCA or anti-neutrophil cytoplasmic antibody and plasmapheresis or plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE'S SYNDROME)

Incidence: 1 per 100,000/year	Procedure	Recommendation	Category
	TPE	Grade 1A	I** (dialysis independent)
	TPE	Grade 1B	I** [diffuse alveolar hemorrhage (DAH)]
	TPE	Grade 1A	IV** (dialysis dependent; no DAH)

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
1 (17)	0	17 (430)	17	Type I

**See technical notes

Description of the disease

Anti-glomerular basement membrane disease is one cause of the clinicopathologic entity, rapidly progressive glomerulonephritis (RPGN). RPGN consists of rapid loss of renal function with the histologic finding of crescent formation in over 50% of glomeruli. These crescents represent a proliferation of cells within Bowman's space of the glomerulus due to the extravasation of proteins into this space. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes.

RPGN is NOT A SINGLE DISEASE ENTITY but is a clinical syndrome that can result from a number of etiologies. RPGN is divided into three categories based on the immunoflourescence pattern on renal biopsy. These categories are:

1) Linear deposits of IgG due to autoantibodies to type IV collagen representing anti-glomerular basement membrane GN (anti-GBM). It accounts for 15% of cases.
2) Granular deposits of immune complexes caused by a variety of GNs including post-streptococcal GN, Henoch-Schönlein purpura, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis. Immune-complex RPGN accounts for 24% of cases of RPGN. (See fact sheet on immune-complex RPGN).
3) Minimal immune deposits in the glomerulus with the presence of anti-neutrophil antibodies (either C-ANCA or P-ANCA) in the serum. This pauci-immune RPGN, also referred to as ANCA-associated RPGN, is seen in Wegener's granulomatosis (WG) and microscopic polyangiitis (MP) and accounts for 60% of RPGN cases. (See fact sheet on ANCA-associated RPGN).

It is important for apheresis medicine practitioners to identify the specific category of RPGN present in their patient as TPE treatment protocols and responses differ among the three categories.

Clinically, anti-GBM consists of RPGN and diffuse alveolar hemorrhage (DAH), though 30–40% of patients will have only renal involvement. The pulmonary symptoms range from breathlessness to overt hemoptysis. Chest radiograph is the most useful tool in demonstrating DAH but the findings are nonspecific. Anti-GBM is associated with a specific HLA allele, DRB1*1501. DAH is associated with exposure to hydrocarbons, chemical compounds, cocaine, marijuana, hard metal dust, fire smoke, and cigarette smoking. Almost all patients have anti-GBM antibodies detectable in their blood. This antibody is directed toward the α3 chain of type IV collagen, which is found in renal and alveolar basement membrane. In addition, 30% of patients will also have detectable ANCA. Patients exhibiting both antibodies behave more like anti-GBM than ANCA-associated RPGN in the short-term but more like ANCA-associated RPGN in the long-term.

Current management/treatment

In anti-GBM, the current treatment is the combination of TPE, cyclophosphamide, and corticosteroids. In general, the disease does not relapse and therefore patients do not require chronic immunosuppression. The exception is those patients who have ANCA in addition to anti-GBM antibodies. These patients respond rapidly to treatment, like anti-GBM, but can relapse, like ANCA-associated RPGN. These patients require long-term immunosuppression.

Rationale for therapeutic apheresis

Because of the knowledge that the disorder was associated with the presence of autoantibodies and the poor prognosis of the disorder with treatments available at the time, TPE was applied to the disorder in the early 1970s. A large number of case reports and case series have appeared. A single randomized prospective trial involving a small number of patients has been reported and demonstrated improved survival of both the patients and their kidneys.

Anti-GBM is predominantly a disease of adults but there have been reports of children as young as 12 months of age being affected by the disorder. These have been in the form of case reports so limited data is available concerning the behavior of the disorder in this patient population. These patients have been treated similarly to adult patients.

Technical notes

It is critical that TPE is implemented early in the course of anti-GBM disease. Several series have demonstrated that most patients with creatinine less than 6.6 mg/dL recover renal function. Those with an initial creatinine above 6.6 mg/dL or who are dialysis dependent at the time of initiation of TPE will not recover renal function due to irreversible glomerular injury. Such patients do not benefit from TPE and it should not be performed unless DAH is present. DAH can be rapidly fatal, may have relatively mild manifestations, and responds to TPE in 90% of affected patients. Therefore, a low threshold for initiating TPE is warranted in the presence of DAH. When present, plasma should be used for the last portion of the replacement fluid. Of note, some studies have found that patients with DAH but no renal involvement do well irrespective of the use of TPE.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin, plasma	

Duration and discontinuation/number of procedures

In most patients undergoing TPE and immunosuppression, anti-GBM antibodies fall to undetectable levels within 2 weeks and the minimum course of TPE should be 14 days. The presence or absence of antibody itself should not be used to initiate or terminate therapy, because antibody is not demonstrable in a small percentage of people with the disease and the antibody may be present in patients without active disease. In those patients with active disease, TPE should continue until resolution of evidence of ongoing glomerular or pulmonary injury.

References [118–123]

*As of October 8, 2009 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and anti-basement antibody disease for articles published in the English language. References of the identified articles were searched for additional cases and trials.

APLASTIC ANEMIA; ACQUIRED PURE RED CELL APLASIA

Incidence: AA: 0.2 per 100,000/year	Procedure	Recommendation	Category
PRCA: rare, exact number not known	TPE	Grade 2C	III (AA)
	TPE	Grade 2C	II (PRCA)

# of reported patients*: <100

	RCT	CT	CS	CR	Type of evidence
Aplastic Anemia	0	0	2 (6)	5 (5)	Type III
Pure Red Cell Aplasia	0	0	2 (7)	19 (26)	Type III

Description of the disease

Aplastic anemia (AA) and pure red cell aplasia (PRCA) are rare hematopoietic stem cell disorders. AA involves all cell lines and is defined as marked pancytopenia in the peripheral blood and a hypocellular bone marrow in the absence of clonal hematopoiesis, abnormal cellular infiltration or increased reticulin fibrosis. PRCA selectively involves erthyroid precursors and is characterized by normochromic normocytic anemia, reticulopenia (reticulocyte count <1%), and an almost complete absence of marrow erythroblasts but with normal production of myeloid cells and platelets. Thus, it is presumed that the defect lies within erythroid precursors in PRCA versus within the stem cells in AA. Most cases of AA and PRCA are acquired, however unusual inherited forms exist. Acquired disease can be primary (idiopathic) or secondary to a variety of neoplastic, autoimmune or infectious diseases or certain drugs and chemicals. Chronic infection and lysis of erythroid progenitors by parvovirus B19 may cause PRCA in immunocompromised individuals (e.g. AIDS patients).

Acquired PRCA may result from immune-mediated injury of erythroid progenitor cells by IgG antibodies or cytotoxic T lymphocytes (CTLs), production of soluble products, such as inhibitory or proapoptotic cytokines, by CTLs, or anti-erythropoietin antibody. PRCA occurs in ≤20% of patients after a major ABO mismatched allogeneic hematopoietic stem cell transplant, and is usually related to persistent host anti-donor isohemagglutinins that suppress erythroid precursors in the engrafting marrow. It is more commonly observed following the use of nonmyeloablative conditioning regimens. Immune-mediated mechanisms of acquired AA involve CTLs, marrow-suppressive cytokines, cell cycle blockade and apoptosis. Primary acquired PRCA may present at any age with symptoms of severe anemia. Acquired AA occurs most commonly between the ages of 15-25 with a second smaller peak after age 60. Certain HLA loci (e.g. HLA DR2) are associated with AA. The disease can develop abruptly over days or insidiously over weeks to months. AA is classified according to the degree of peripheral blood pancytopenia. Severe AA is defined as bone marrow cellularity <30% and two of three peripheral blood criteria: Absolute neutrophil count (ANC) <500/μL, platelet count <20,000/μL or reticulocyte <40,000/μL (<1%) and no other hematologic disease. Most patients with AA present with symptoms related to bleeding (most frequent), anemia and/or infection.

Current management/treatment

For both AA and PRCA, underlying triggering etiologies, such as malignancies or infections, should be sought and treated and possible offending drugs (including erythropoietin in PRCA) should be discontinued. IVIG is indicated for chronic active parvovirus B19 virus infection in immunocompromised patients with PRCA and surgical resection may be curative for PRCA associated with thymoma. For other etiologies, the current approach to therapy includes replacement of defective hematopoiesis by stem cell transplantation, or suppression of an apparent autoimmune process.

Allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA matched sibling donor is the treatment of choice for severe AA in newly diagnosed patients <40 years of age. Overall, the survival rates reported from major centers are approximately 70%. Older patients with AA or younger patients with mild disease or lacking a matched donor are treated with anti-thymocyte globulin (ATG) and cyclosporine A. Hematopoietic growth factors and androgens are often used as adjunctive therapies.

Primary acquired PRCA is usually responsive to immunosuppressive therapy. Corticosteroids (prednisone at 1 mg/kg) are used as first line therapy and are associated with significant response rates (~40%). Alternative treatment is required if no response is achieved after 2-3 months. Salvage agents include cyclophosphamide, azathioprine, cyclosporine, ATG, rituximab, alemtuzumab and high-dose IVIG. No data exist favoring one salvage agent over the other. Matched sibling donor allogeneic HSCT results in restoration of normal hematopoiesis in cases of refractory and relapsed PRCA, suggesting graft-versus-autoimmunity as a likely mechanism for response.

Rationale for therapeutic apheresis

Because these diseases may be immunologically mediated, TPE may be helpful by removing serum antibody and/or inhibitory activity. Case reports of benefit with TPE for AA consisted of patients who had concomitant autoimmune diseases. TPE is therefore reasonable to consider for such patients with severe AA who do not have a transplant option and have failed to respond to conventional immunosuppressive therapy. TPE may also improve PRCA developing after major ABO-mismatched allogeneic HSCT or in the setting of erythropoietin therapy and anti-erythropoietin antibodies. Regarding PRCA after major ABO-mismatched HSCT, a recent report suggests that PRCA could be prevented by performing TPE prior to transplantation and three other reports suggest benefit using immunoadsorption apheresis.

Technical notes

See the introduction to this article.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin, plasma	

Duration and discontinuation/number of procedures

Until recovery of hematopoiesis or adequate red cell production. No well-defined treatment schedules exist, however 1-24 treatments were reported in the literature.

For PRCA, usually a minimum of 2-3 weeks and occasionally for much longer until a response occurs.

References [124–134]

*As of September 17, 2009 using PubMed and the MeSH search terms aplastic anemia, pure red cell aplasia, plasmapheresis and therapeutic plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

AUTOIMMUNE HEMOLYTIC ANEMIA: WARM IDIOPATHIC HEMOLYTIC ANEMIA; COLD AGGLUTTIN DISEASE

Incidence: 1 per 100,000/year	Procedure	Recommendation	Category
	TPE	Grade 2C	III WAIHA
	TPE	Grade 2C	II CAD (life threatening)

# of reported patients: <100

	RCT	CT	CS	CR	Type of evidence
WAIHA	0	0	1 (3)	19 (20)	Type III
CAD	0	0	2 (6)	19 (22)	Type III

Description of the disease

Autoimmune hemolytic anemia (AIHA) represents a group of disorders in which autoantibodies mediate either intravascular red cell destruction by the terminal lytic complex (C5b-C9) or, more often, extravascular destruction in the spleen by the macrophage-phagocytic system. The presenting symptoms include fatigue and jaundice. The laboratory findings are of hemolysis (anemia, hyperbilirubinemia, elevated serum LDH, reticulocytosis), as well as a positive direct antiglobulin (Coombs) test. AIHA can be classified into two major types, warm autoimmune hemolytic anemia (WAIHA) and cold agglutinin disease (CAD).

Warm autoantibodies consist of IgG hemolysins that react optimally at 37°C and are directed primarily against the red cell Rh antigens. Causes of WAIHA include: idiopathic (30% of cases), secondary (associated with underlying autoimmune diseases, lymphoproliferative disorders, cancer, or infections) and drug-induced (e.g. methyl-dopa, cephalosporins,). In WAIHA, the direct antiglobulin test is positive with anti-IgG and may additionally be positive with anti-C3.

Cold agglutinin disease (CAD) results from IgM autoantibodies that react optimally at 0-5°C and can be directed against the red cell I/i antigens. It usually arises in reaction to an infection (polyclonal autoantibodies) or to a lymphoproliferative disorder (monoclonal autoantibodies). The cold-reactive IgM autoantibody produced after *Mycoplasma pneumonia* infection usually has anti-I specificity, whereas the autoantibody associated with Epstein-Barr virus infection (infectious mononucleosis) frequently has anti-i specificity. Few cases of tacrolimus induced CAD have been recently described. In CAD, the direct antiglobulin test is positive with anti-C3 only.

The severity of hemolysis in AIHA is determined by the titer of the autoantibody, its avidity for the relevant red blood cell (RBC) antigens, its ability to fix complement, and, for cold autoantibodies, the thermal amplitude. The thermal amplitude is defined as the highest temperature at which the antibody reacts with its cognate antigen. A cold autoantibody with high thermal amplitude could, therefore, be active within a range of temperatures attainable in vivo (e.g. 30-37°C). The thermal amplitude of a cold agglutinin may be more predictive of the severity of hemolysis than its titer.

Current management/treatment

Therapy for WAIHA is typically initiated with prednisone (1-2 mg/kg/day) and continued until response becomes evident. Prednisone suppresses antibody production and down-regulates Fc-receptor-mediated red cell destruction in the spleen. Splenectomy is often recommended for steroid failures. Various immunosuppressive/immunomodulatory agents have been used for patients with refractory hemolysis; rituximab has recently shown promise. Treatment for CAD, on the other hand, is often not necessary because of the relatively ineffective mechanisms of cellular destruction initiated by cold agglutinins (particularly true in infection-related CAD). If indicated by more severe hemolysis/anemia, treatment primarily involves avoiding exposure to cold. Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction of C3b-sensitized red cells. A recent prospective phase II study showed 54% response rate in 27 CAD patients treated with 37 courses of rituximab.

Rationale for therapeutic apheresis

TPE may remove pathogenic immune complexes, activated complement components and circulating autoantibodies. TPE is considered in AIHA to reduce/eliminate autoantibody in severe situations: i.e. patients who are not responding to transfusion and are in critical condition because of fulminant hemolysis. Apheresis treatment may buy time until immunosuppressive therapy takes effect or if other treatments have failed. IgG is mostly extravascular and is absorbed to the RBC at body temperature and thus not efficiently removed when plasma is removed. Anecdotal evidence of favorable results has been described in some cases of IgG hemolysis. IgM, on the other hand, is mostly intravascular and binds poorly to RBC at body temperature thus TPE may significantly reduce antibody titer in CAD. In either case, improvement of AIHA after TPE is usually temporary, depending on the characteristics and rate of production of the autoantibody and thus should be combined with concomitant immunosuppressive therapy. Case reports have claimed success using TPE as a ''primer'' for IVIG or cyclophosphamide treatment (e.g. synchronization of three daily sessions of TPE followed by pulse treatments with cyclophosphamide and prednisone).

A recent nonrandomized study showed significantly higher hemoglobin increments per unit transfused in AIHA patients who did **not** receive TPE; hemoglobin levels were not improved by TPE in the patients who did. Thus the role of TPE in AIHA remains uncertain. The rational seems clear but clinical data are limited to case reports that do not always show improvement.

Technical notes

If the thermal amplitude of an IgM cold autoantibody is such that agglutination occurs at room temperature, red cell agglutination may occur within the cell separator and tubing. In these situations, therapy may require a controlled, high temperature setting of 37°C both in the room and within the extracorporeal circuit.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

Until the hemolysis is controlled and the need for transfusions is limited or until drug therapy takes effect.

References [135–144]

*As of September 9th, 2009 using PubMed and the MeSH search terms autoimmune hemolytic anemia, cold agglutinin disease, plasma exchange and plasmapheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.

BABESIOSIS

Incidence: rare (fewer than 0.1 per 100,000/year); it is an endemic infection in the northeast and great lakes regions of USA	Procedure	Recommendation	Category
	RBC exchange	Grade 1B	I (severe)
	RBC exchange	Grade 2C	II (high risk population)

# of reported patients*: < 100

RCT	CT	CS	CR	Type of evidence
0	0	3 (14)	13 (14)	Type II-3

Description of the disease

Human babesiosis is an emerging tick-borne infectious disease caused by an intraerythrocytic protozoan. The four babesia species that most commonly infect human are: *B. microti*, the predominant U.S. pathogen, *B. duncani, B. divergens and B. venatorum*. Endemic areas are the coastal and inland regions of the northeast, as well as northern Midwest particularly Wisconsin and Minnesota.

The disease is usually transmitted from an animal reservoir to humans by the bites of ixodid ticks, most commonly between May through October. Rarely babesiosis is acquired by transfusion of contaminated blood products, typically fresh or frozen packed red blood cells (RBCs) from asymptomatic blood donors. Several cases of neonatal babesiosis acquired by transplacental transmission have been reported. The incubation period is usually 1-3 weeks, with longer incubation period (6-9 weeks) reported with transfusion transmission.

Three distinct syndromes have been described: 1. Asymptomatic infection, as suggested by the disparity between seroprevalence and the number of reported cases. It is uncertain whether patients experiencing asymptomatic babesial infection are at risk for any complications. 2. Mild-moderate illness, most common presentation, characterized by the gradual onset of malaise and fatigue followed by intermittent fever and one or more of the following: chills, sweat, anorexia, headaches, myalgia, arthralgia and cough. The illness usually lasts for several weeks to months, occasionally with prolonged recovery that can last more than a year. 3. Severe disease which generally occurs in people with underlying immunosuppressive conditions that include HIV, malignancy, immunosuppressive medication, and splenectomy. Other risk factors include: age $\geq$50 and simultaneous infection with Lyme disease. Severe disease symptoms may include acute respiratory failure, disseminated intravascular coagulation (DIC), congestive heart failure, acute liver and renal failure, and hemolytic anemia. Excessive cytokine production is thought to be a major cause of severe babesiosis and is associated with tissue pathology that can lead to significant end-organ damage and can result in persistent relapsing disease or death.

Laboratory testing is required for diagnosis. Specific diagnosis is made through microscopic identification of the organism using Giemsa-stained thin blood smear, DNA amplification using polymerase chain reaction or serologic testing using indirect immunoflurescent assay (IFA). The detection of IgM is indicative of recent infection while IgG titer of 1:1024 or greater usually signify active or recent infection. Titers generally return to 1:64 or less within 8 to 12 months but may persist for years. 1-10% of the RBCs are parasitized in normal hosts, but seldom exceeds 5%. In immunocompromised host, parasitemia up to 85% was described.

Current management/treatment

Primary therapy for mild to moderate disease includes antibiotic combination. Most people can be successfully treated with atovaquone and azithromycin administered for 7 to 10 days. Combination of quinine sulfate and clindamycin, the first drug combination used in this disease, is equally effective but associated with more adverse reactions. Thus, this combination should be used when patients do not respond well to atovaquone and azithromycin. In severe disease, the combination of quinine sulfate and clindamycin, given 7-10 days is the treatment of choice. RBC exchange is indicated for all babesiosis patients with heavy parasitemia ($\geq$10%) or who have significant comorbidities such as significant hemolysis, DIC, pulmonary, renal, or hepatic compromise. In persistent relapsing disease, antibiotics should be given for a minimum of six weeks and for at least two weeks after the last positive blood smear. Due to high morbidity and mortality rate associated with *B. divergens* infections, it is recommended that these infections be treated with RBC exchange, clindamycin and quinine.

Rationale for therapeutic apheresis

The use of RBC exchange in babesiosis reflects the larger experience with its use in malaria. Three mechanisms of action by which RBC exchange might influence the course of the disease are possible. First, it helps to lower the level of parasitemia by physically removing the infected RBCs from the blood stream and replacing them with non-infected RBCs. Because babesia organisms do not have an exo-erythrocytic phase, removal of RBC-associated parasites might be very effective. Second, by removal of rigid infected cells, RBC exchange could decrease obstruction in the microcirculation and tissue hypoxia caused by adherence of RBCs to vascular endothelium. Finally, the hemolytic process produces vasoactive compounds, including a variety of cytokines (including INF-γ, TNF-α, IL-1, IL-6), nitric oxide and thromboplastin substances, which can promote renal failure and DIC. RBC exchange may help to remove the proinflammatory cytokines.

The greatest advantage of RBC exchange over antibiotic therapy is its rapid therapeutic effectiveness. In severe cases, the benefits seem to clearly outweigh the risks of the procedure, mainly, exposure to multiple RBC transfusions.

Technical notes

Automated apheresis instruments calculate the amount of RBCs required to achieve the desired post-procedure hematocrit, fraction of red cells remaining and, by inference, the estimated final parasite load. A single two-volume RBC exchange can reduce the fraction of remaining patient red cells to roughly 10-15% of the original. In critically ill patients who failed antimicrobials and/or RBC exchange, the use of TPE has been also reported.

For patients with severe coagulopathy, plasma may be incorporated into replacement fluid, either by performing whole blood exchange or TPE.

Volume treated: 1 to 2 total RBC volume	**Frequency:** single procedure but can be repeated
Replacement fluid: leukoreduced RBCs.	

Duration and discontinuation/number of procedures

The specific level of parasitemia to guide when to perform RBC exchange is not clear. 10% is the most common used guideline as well as severe symptoms. The specific level to which parasitemia must be reduced to elicit the maximum therapeutic effect is not defined. Treatment is usually discontinued after achieving <5% residual parasitemia. Decision to repeat the RBC exchange depends on the level of parasitemia post-exchange as well as the clinical condition (ongoing signs and symptoms).

References [145–156]

*As of September 23, 2009 using PubMed and the MeSH search terms Babesiosis and erythrocytapheresis, red cell exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

BURN SHOCK RESUSCITATION

Incidence: unknown				Procedure	Recommendation	Category
				TPE	Grade 2B	IV

# of reported patients*: <100

RCT	CT	CS	CR	Type of evidence
1 (17)	0	5 (65)	NR	Type II-2

Description of the disease

Major thermal injury, which involves greater than 25% total body surface area (TBSA), results in clinically significant, potentially fatal physiologic consequences. Increased capillary permeability and intravascular volume deficits predispose to cellular shock due to diminished perfusion of major organs. Disruption of the sodium-potassium membrane pump results in an intracellular sodium shift contributing to the progressive hypovolemia. Heat injury causes release of inflammatory mediators, including complement, kinins, and histamine, with subsequent vasodilation and capillary leakage. Myocardial depression with decreased contractility and inappropriate cardiac output may be associated with hemodynamic fragility. Acute Respiratory Distress Syndrome may complicate the clinical picture whether related to inhalational injury or excessive edema with increasing fluid resuscitation attempts. Affected patients have suppressed leukocyte chemotactic function and lymphocyte suppression, both of which contribute to susceptibility to life threatening infections, in addition to the loss of the important barrier of normal skin. Circulating mediators have been implicated in majority of these physiologic derangements although the exact mechanisms or humoral ''factor(s)'' remain enigmatic. Decreased levels of fibronectin in severely burned patients have been correlated with impaired function of the reticuloendothelial system and phagocytosis. Microembolization of tissue debris, bacteria, and byproducts of disseminated intravascular coagulation are other potential contributors to the pathophysiology of burn shock.

Current management/treatment

The mainstay of treatment in the immediate post-burn period is aggressive intravenous fluid resuscitation. Practice guidelines published by the American Burn Association indicate that the volume of fluid resuscitation is based on estimated of body size, surface area and extent of burns, typically 2-4 ml/kg body weight/%TBSA of crystalloid in the first 24 hours. Goals of fluid replacement are to maintain urine output while balancing risks of edema, ARDS and hypoperfusion of vital organs. Fluid resuscitation is successful in the majority of burn patients. Patients with full-thickness burns, inhalation injury or delay in resuscitation may have greater fluid requirements. The most common solution is lactated Ringers; other solutions such as hypertonic saline, or colloids such as 5% albumin or hydroxyethyl starch, are also incorporated into different fluid resuscitation strategies.

Rationale for therapeutic apheresis

Enthusiasm for the theoretical benefit of TPE in the setting of acute burn shock was based on the removal circulating factors such as inflammatory mediators, or other humoral substances participating in the pathophysiology of major burn injury. Replacement with donor plasma hypothetically could facilitate decrease in capillary permeability, and improve intravascular oncotic pressure, which might improve response to fluid resuscitation, urine output, and possibly immune function. Although the specific mediators of burn injury in the circulation are not precisely characterized, the literature implicates circulating component(s). For example, cross perfusion studies from burned to unburned dogs caused a decrease cardiac output in the unburned animals; in vitro studies from the sera of human burn patients demonstrate that specific immune cellular abnormalities can be reversed when the cell is removed from the burn environment, such as placement in plasma from a healthy individual.

TPE did not alter the course of burn shock in the single published randomized control trial of 17 patients. There were 3 deaths in the TPE group versus none in the control group. Of the limited published case series, a variety of favorable physiologic effects were reported with respect to fluid resuscitation, urine output, cardiac function and immune benefits. Clinical outcome data were not consistently available. In one case series, TPE was applied in 5 clinical settings (number of surviving patients/total number of patients treated): failed fluid resuscitation (9/10), myoglobinuria (2/3), respiratory failure ARDS (3/4), metabolic exhaustion (4/6), and documented sepsis (1/5); however, the endpoint for clinical follow-up was not defined in this study. Overall mortality with TPE was 33% without a control group for comparison.

Further investigation with well-designed randomized controlled trials would be needed to establish the efficacy and safety of TPE in this setting. The American Burn Association acknowledges that TPE is sometimes applied empirically as a salvage therapy; however, it does not recommend TPE outside the context of a clinical trial.

Technical notes

When performed in the published studies, TPE was instituted early in the post-burn period, typically 8 to 16 hours after injury. Patients treated with TPE had greater than 40-50% TBSA burns and were refractory to fluid resuscitation attempts. In some select patients with continued hemodynamic instability and sepsis, TPE was employed 1 week or more after the time of initial injury. TPE adverse reactions were infrequently reported in these studies although it is not clear if this was related to absence of adverse reaction reporting in the case study design or true tolerance of the TPE procedure.

Volume treated: 1.5 TPV	**Frequency:** once, see below
Replacement fluid: plasma	

Duration and discontinuation/number of procedures

Most reports involved performing one TPE within the first 24 hours (8-16 hours) post-burn with additional 1 or 2 TPE procedures in select patients.

References [157–167]

*As of January 9, 2010 using PubMed and journals published in English language using the search terms burn(s), shock, therapeutic plasma exchange, plasmapheresis. References of the identified articles were searched for additional cases and trials.

CARDIAC ALLOGRAFT REJECTION

Incidence: Cellular rejection: 30-50% of transplant recipients in first year. Antibody mediated rejection (AMR): 3-15% of transplant recipients.	Procedure	Recommendation	Category
	ECP	Grade 1A	I (prophylaxis)
	ECP	Grade 1B	II (treatment of cellular rejection)
	TPE	Grade 2C	III (treatment of AMR)

# of reported patients*: 100-300 (ECP); 100-300 (TPE)

	RCT	CT	CS	CR	Type of evidence
ECP; prophylaxis	2 (98)	2 (26)	3 (16)	1 (1)	Type I
ECP; rejection treatment	1 (16)	0	4 (57)	2 (4)	Type II-3
TPE; AMR treatment	0	0	9 (132)	4 (8)	Type II-3

Description of the disease

The first successful heart transplant was performed in 1967. Thanks to potent immunosuppression, survival and quality of life have improved since then, although infection, malignancies, and allograft rejection continue to threaten long-term survival. Cardiac allograft rejection may be hyperacute (in cases of ABO or major HLA incompatibility), acute cellular (ACR), acute antibody-mediated (AMR) or chronic (allograft vasculopathy). ACR is the most common and is mediated by T cells. The diagnosis of ACR is made by histologic examination of surveillance endomyocardial biopsies of the right ventricle, which show inflammation and myocyte damage. ACR is classified according to the International Society for Heart and Lung Transplantation (ISHLT) grading system from 0R to 4. AMR is mediated by B lymphocytes and is more likely to cause hemodynamic instability with or without histologic evidence of immunoglobulin and/or complement deposition in the tissue. AMR is also suspected when there is interstitial edema, prominent endothelial cells lining the cardiac microvasculature and intravascular histiocytes. Often, the only sign of AMR is decreased ventricular ejection fraction. The prognosis of AMR is worse than ACR; AMR is a strong risk factor for the early development of allograft vasculopathy. Young age, female gender, history of congenital heart disease, high titer of HLA antibodies, positive pretransplant crossmatching, sensitization to OKT3, or prior exposure to cytomegalovirus increase the risk of AMR. AMR and ACR may be seen alone or in combination. Chronic rejection or allograft vasculopathy occurs months to years after transplant and its mechanism is poorly understood. It is characterized by progressive intimal thickening of the coronary arteries leading to late graft failure.

Current management/treatment

The approach to rejection prophylaxis in heart transplantation is based on three principles: a) the period with the highest risk for rejection is within the first 3-6 months posttransplant when immune reactivity is strongest; b) lower doses of several drugs or combinations of drug and apheresis is preferable to large doses of a single agent in order to minimize side-effects; and c) drug-induced profound immunosuppression carries serious side-effects such as infection and malignancy. Induction therapy with antilymphocyte antibodies is used by many transplant centers in the early postoperative period. Maintenance immunosuppression uses three classes of drugs: calcineurin-inhibitor (cyclosporine or tacrolimus), antiproliferative agent (mycophenolate mofetil or azathioprine) and corticosteroids. In addition to drug-specific side effects, cardiac allograft recipients have a high risk of developing infections, the major cause of death in the first post-transplant year. There is also an increased lifetime risk of immunosuppression induced malignancies reaching 35% at 10 years post-transplant. Malignancy is the second most common cause of death, behind allograft vasculopathy, in patients who survive 5 years following transplant. Non-melanoma skin cancers are the most prevalent, followed by post-transplant lymphoproliferative disorder (PTLD) and Kaposi's sarcoma.

Rationale for therapeutic apheresis

Apheresis techniques have both complemented and helped avoid the use of drugs to prevent and/or manage cardiac allograft rejection. Although the mechanism of ECP remains unknown, it is postulated that it stimulates the immune system to destroy clone-specific T cells causing allograft rejection (''transimmunization'') and induces immunotolerance via expansion of regulatory T cells (Tregs). Tregs are CD4+CD25+ lymphocytes that suppress immune reactions in an antigen-specific fashion. The number of circulating Tregs in transplant patients treated with ECP has been shown to double compared with pre-ECP, a phenomenon that persisted for up to a year after cessation of treatments. In contrast, patients receiving only immunosuppressive drugs had very low Treg numbers. Importantly, ECP does not increase infection risk. The goal of TPE is to remove donor-specific antibodies and/or inflammatory mediators implicated in AMR. Thus, while ECP is used on a chronic basis as an immunomodulatory approach, TPE's role is in the acute setting of rejection. Although there have been controlled trials of ECP in heart transplant recipients, the experience with TPE is limited to retrospective review of outcomes.

Technical notes

In patients weighing <45 kg, ECP requires protocol adjustments to compensate for the extracorporeal volume during the collection phases of the procedure. Although there are no data that a minimum number of lymphocytes need to be treated to mediate the benefits of ECP, it is advisable to check a CBC prior to the procedure to ensure that there are circulating lymphocytes. Lymphopenia due to immunosuppressants is common in this patient population.

Volume treated: ECP: An MNC product of 200 - 270 mL. The two step process method collects and treats MNCs obtained from 2-times TBV processing. TPE: 1 to 1.5 TPV	**Frequency:** ECP: Two procedures on consecutive days (one series) weekly or every 2 to 8 weeks for several months (regimens vary widely).
Replacement fluid: ECP: NA, TPE: albumin; plasma	TPE: daily for a minimum of 3 days

Duration and discontinuation/number of procedures

The largest randomized clinical trial of ECP treated patients with 24 series during the first 6 months following transplantation and demonstrated decreased risk of cardiac rejection. The second largest study showed significant reduction of vasculopathy with one ECP series every 4 to 8 weeks for 2 years. Beyond these data, there are no criteria for duration or discontinuation of ECP or TPE.

References [168–177]

*As of January 1, 2010 using PubMed and journals published in the English language using the search terms heart transplant, cellular rejection, humoral rejection, transplant vasculopathy, ECP, photopheresis, plasmapheresis, and therapeutic plasma exchange (TPE). References of the identified articles were searched for additional cases and trials.

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Incidence: Very rare (282 cases in CAPS Registry)				Procedure	Recommendation	Category
				TPE	Grade 2C	II

# of reported patients*: 100–300**					
RCT	CT	CS	CR	Type of evidence	
0	0	6 (60)	29 (33)	Type III	

**According to the CAPS Registry, 109 patients have received TPE.

Description of the disease

The antiphospholipid syndrome (APS) is an acquired hypercoagulability condition characterized by one or more episodes of venous and/or arterial thrombosis and/or obstetric complications in a patient with laboratory evidence of antiphospholipid antibodies, anticardiolipin and/or anti-β_2-glycoprotein I. Catastrophic antiphospholipid syndrome (CAPS) was first described in 1992 by Asherson, as an uncommon variant of antiphospholipid syndrome that results in multiorgan failure. CAPS is defined as the acute onset of multiple thromboses in at least three organ systems over a period of days or weeks, in patients with antiphospholipid antibodies. The sites most commonly affected by thrombosis are small vessels of the kidneys, lungs, brain, heart and skin, although large vessel thrombosis may also occur. Common manifestations of CAPS include renal failure, acute respiratory distress syndrome, pulmonary embolism, livedo reticularis, purpura, skin necrosis, cerebral infarcts, encephalopathy, seizures, and cerebral venous occlusion. In addition, the systemic inflammatory response syndrome (SIRS) is a component of the acute phase of CAPS. CAPS may be the first manifestation of APS (''de novo'') or complicate the course of patients known to have the syndrome. It is unknown why a minority of patients with APS present with a catastrophic picture. In the CAPS Registry, 53% of the patients are presumed to have precipitating factors which preceded the clinical diagnosis of CAPS: infection was the most common finding, affecting 22% of the patients, followed by surgical procedures at 10%, warfarin withdrawal or low international normalized ratio (INR) (8%), medications (7%), obstetric complications (7%), neoplasia (5%) and systemic lupus erythematosus (SLE) flare (3%). Mortality approaches 50% and is mainly due to myocardial thrombosis with or without respiratory failure. Thrombocytopenia can be marked and 20% of CAPS patients present with disseminated intravascular coagulation (DIC). Over 33% of patients have hemolysis which is secondary to DIC or Coombs positive immune hemolysis. However, schistocytes are only rarely seen, and help differentiate CAPS from other thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). More than 80% of patients with CAPS have serological evidence of lupus anticoagulant and IgG anticardiolipin antibodies. IgM is seen in less than 40% of cases.

Current management/treatment

The optimal treatment of CAPS is still debatable since there have been no prospective studies due to the rarity of the condition. However, the therapeutic approach has three clear aims: treat any precipitating factors (i.e., infection, necrotic organ, etc), prevent and control ongoing thrombosis, and suppress the excessive cytokine production. Cervera et al recently published a review of outcomes of 280 patients entered into the CAPS Registry (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM). They found that 44% did not survive the acute episode and that recovery was significantly associated with the use of anticoagulants (63% versus 22%, p < 0.0001; odds ratio [OR] 6, 95% confidence interval [95% CI] 2.8–13.8). The authors also noted that most patients received multiple treatments and that the combination with the best outcome was anticoagulants, corticosteroids, and TPE and/or IVIG. Although some patients also received cyclosphosphamide to halt antibody production, the data are not conclusive about its role in CAPS unless the patient has a flare of SLE.

Rationale for therapeutic apheresis

The exact mechanism of TPE in CAPS is not known, but the removal of antiphospholipid antibodies as well as cytokines, tumor necrosis factor-α, and complement is likely to play an important role. Furthermore, since plasma has been used as the replacement fluid in the majority of reported cases, transfusion of natural anticoagulants such as antithrombin and proteins C and S are likely to contribute to the overall benefit of the procedure. Two successful cases treated with albumin as replacement fluid claim that plasma may not be always necessary in CAPS. Since plasma antithrombin level is essential to mediate anticoagulation with heparin, the use of albumin alone as replacement fluid may prevent the beneficial effect of heparin unless levels of antithrombin are serially monitored and heparin anticoagulation is proven by laboratory monitoring. Thus, it is likely that a combination of plasma and albumin would provide the necessary benefit of TPE and minimize potentially serious and undesirable side-effects transfusion reactions from multiple units of plasma.

Technical notes

Plasma was used in most reported cases; efficacy of albumin has not been widely tested.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily
Replacement fluid: plasma (used in most reported cases; efficacy of albumin not tested)	

Duration and discontinuation/number of procedures

Most patients whose cases have been published received daily TPEs for a minimum of 3 to 5 days. The patient's clinical response dictates the use of TPE; no single clinical or laboratory parameter is used to determine when to discontinue treatment. Some patients have been treated for weeks instead of days.

References [178–191]

*As of January 9, 2010 using PubMed and journals published in English language using the search terms catastrophic antiphospholipid syndrome (CAPS), antiphospholipid syndrome, lupus anticoagulant, anticardiolipin antibodies, therapeutic plasma exchange, plasmapheresis. References of the identified articles were searched for additional cases and trials.

CHRONIC FOCAL ENCEPHALITIS (RASMUSSEN'S ENCEPHALITIS)

Incidence: rare			Procedure	Recommendation	Category:
			TPE	Grade 2C	II
			IA	Grade 2C	II

# of reported patients*: <100

	RCT	CT	CS	CR	Type of evidence
TPE	0	0	2 (9)	3 (5)	Type II-3
IA	0	0	1 (3)	1 (1)	Type II-3

Description of the disease:

This syndrome of chronic encephalitis was originally described in three children by Theodore Rasmussen in 1958. The hallmarks of the syndrome are intractable focal seizures (epilepsia partialis continua) resistant to anticonvulsant drugs, and progressive unilateral cerebral atrophy leading to progressive hemiparesis, loss of function in the affected cerebral hemisphere and cognitive decline. Patients may exhibit recurrent status epilepticus. Onset is typically in childhood (mean age 6.8 ± 5.1 years) but a similar syndrome has been described in adults. The etiology is unknown, but antecedent infection with Epstein-Barr virus, herpes simplex, enterovirus, or cytomegalovirus has been implicated. Cytomegalovirus genome has been found in resected cortical tissue of 3 adult patients with Rasmussen's encephalitis. Cerebrospinal fluid analysis is typically normal, although mild lymphocytic pleocytosis and elevated protein may be found.

Current management/treatment

Anticonvulsants are necessary, but not always effective, nor do they arrest progression of the disease. Subtotal, functionally complete hemispherectomy may markedly reduce seizure activity in a majority of patients but results in permanent contralateral hemiplegia. Intravenous methylprednisolone and oral prednisone given for up to 24 months in a tapering schedule may help to diminish epilepsia partialis continua and motor deficits during the first year of onset and before hemiplegia develops. Intravenous immunoglobulin (IVIG up to to 2g/kg over 2-5 days, then repeated monthly if there is a response) may be tried prior to a trial of steroids in patients with established disease and may modestly improve the hemiparesis. Some authors recommend intravenous methylprednisolone (400 mg/m^2 every other day for 3 infusions followed by monthly infusions for the first year) and prednisone (2 mg/kg/day tapered over 1 to 2 years) if further treatment is needed. Intraventricular interferon-α given via Omaya reservoir, intravenous rituximab and tacrolimus have been investigated for control of epileptic and neurological aspects of Rasmussen's syndrome.

Rationale for therapeutic apheresis

Patients may have autoantibodies, against several neural molecules, that may be produced in the CNS after cytotoxic T cell-mediated neuronal damage. The demonstration of serum immunoreactivity to the glutamate receptor GluR3 in 3 individuals with histologically confirmed Rasmussen's syndrome led to the use of therapeutic plasma exchange (TPE) in a 9-year-old girl. An initial 7 single-volume TPE procedures over 3 weeks followed by weekly TPE for 4 weeks resulted in marked reduction in GluR3 immunoreactivity and significant clinical improvement (decreased frequency of seizures, resumption of playing with dolls and riding a bicycle) during the first 7 weeks of treatment. Serum GluR3 immunoreactivity spontaneously rose over the subsequent 4 weeks and she deteriorated clinically but had transient responses to repeat course of therapy. More recent reports indicate that serum GluR3 immunoreactivity is a feature of epilepsy syndromes and not specific to Rasmussen's encephalitis, but other brain autoantibodies have been identified in Rasmussen's encephalitis patients. Clinical and EEG parameters of epileptogenesis were transiently diminished by TPE in two other patients. Monthly courses of plasma immunoadsorption using staphylococcal protein A diminished seizure frequency and halted cognitive deterioration in a 16-year-old girl with IgG anti-GluR3 antibodies over a 2-year period, and controlled status epilepticus in a 20-year-old woman. Despite the paucity of clinical reports, investigators in the field recommend a concerted trial of immunotherapy, including apheresis, to control seizures, mitigate functional decline, and delay the need for hemispherectomy in patients with Rasmussen's encephalitis.

Technical notes

Neuropsychological assessment may be helpful in evaluating patients with slowly progressive disease to determine whether TPE is effective in postponing surgical therapy. Protein A column treatment has not been directly compared to TPE. An initial course of TPE may be followed by 2 days of IVIG 1 g/kg. A similar approach may be taken in subsequent courses if a salutary clinical effect is apparent. Note: Since December 2006, devices used to perform protein A immunoadsorption apheresis have not been commercially available in the United States.

Volume treated:	**Frequency:**
TPE: 1 to 1.5 TPV	TPE: 3-6 TPE over 6-12 days; repeat monthly
Protein A Immunoadsorption: 1.5 to 2 TPV	Alternative schedule: TPE weekly
Replacement fluid: albumin/saline	Protein A Immunoadsorption: 1-3, repeat monthly

Duration and discontinuation/number of procedures:

After an initial course of treatment, subsequent courses of TPE (with or without IVIG) may be performed at intervals of 1-2 weeks or up to 2-3 months as empirically needed to maintain clinical stability and avoid or delay hemispherectomy. Immunosuppressive medications may increase the interval between courses. Surgical treatment is offered for the management of patients who exhibit functional or cognitive decline or intractable seizure activity despite intensive immunomodulatory therapy.

References [56,192–202]

*As of August 26, 2009 using PubMed and the MeSH search terms Rasmussen's Encephalitis and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

CHRONIC INFLAMMATORY DEMYLINATING POLYRADICULONEUROPATHY

Incidence: 1-2 per 100,000/year				Procedure	Recommendation	Category
				TPE	Grade 1B	I

# of reported patients*: >300

RCT	CT	CS	CR	Strength of evidence
4 (82)	0	25 (366)	27 (28)	Type I

Description of the disease

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is characterized by proximal and distal symmetrical muscle weakness, with or without numbness, that progresses and relapses for over two or more months. Neurologic impairment includes decreased sensation and diminished or absent reflexes. Cerebrospinal fluid protein is elevated and evidence of demyelination is present on electrophysiological testing. CIDP can occur in conjunction with other disorders such as HIV and diabetes. Patients with monoclonal gammopathies can present with similar findings (see fact sheet on paraproteinemic polyneuropathies). CIDP is distinct from Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy; AIDP) in that it is a chronic rather than an acute disorder (see fact sheet on AIDP). Similar clinical presentations may be seen with inherited, paraneoplastic and toxic neuropathies, and neuropathies associated with nutritional deficiency, porphyria, or critical illness.

Current management/treatment

Corticosteroids, TPE, and intravenous immunoglobulin (IVIG) all yield similar treatment outcomes in controlled trials, therefore a choice among them is based on cost, availability, and side effects. Individuals may differ in response to any one of these agents. Therapeutic response is measured by improvement or stabilization in neurological symptoms, at which point treatment can be tapered or discontinued. 60 to 80% respond to initial therapy but long-term prognosis varies. Maintenance therapy, including continuing steroids, periodic TPE, or repeated infusion of IVIG, is usually required because discontinuation of therapy may be followed by relapse. Maintenance therapy is dictated by the patient's symptoms and clinical exam. Secondary therapies include cyclosporine, interferon, azathioprine, and cyclophosphamide, and other immunosuppressive therapies.

Rationale for therapeutic apheresis

The presumed etiology of CIDP is autoimmune attack on the peripheral nerves. Both humoral and cell-mediated immune responses have been documented. Therapies are aimed at modulation of the abnormal immune response.

Technical notes

See the introduction to this article.

Volume treated: 1 to 1.5 TPV	**Frequency:** 2 to 3 TPE/week until improvement, then taper as tolerated
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

TPE provides short-term benefit but rapid deterioration may occur afterwards. This may necessitate maintenance treatment, with TPE and/or other immunomodulating therapies, which should be tailored to the individual patient. The frequency of maintenance TPE may range from weekly to monthly as needed to control symptoms.

References [56,203–207]

*As of November 2, 2009 using PubMed and the MeSH search terms chronic inflammatory demyelinating polyneuropathy and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

COAGULATION FACTOR INHIBITORS

Incidence: 20-30% in Hemophilia A patients	**Procedure**	**Recommendation**	**Category**
3-5% in Hemophilia B patients.	IA	Grade 2B	III
0.2-1 per 1,000,000/year for spontaneous FVIII inhibitor	TPE	Grade 2C	IV

# of reported patients*: 100-300

	RCT	CT	CS	CR	Type of evidence
IA	0	0	7 (51)	44 (63)	Type II-3
TPE	0	0	7 (83)	36 (39)	Type II-3

Description of the disease

Coagulation factor deficiency can be congenital or acquired due to development of an autoantibody. Patients with moderate to severe congenital FVIII or IX deficiency make alloantibodies following exogenous factor exposure (recombinant or plasma derived). Acquired hemophilia due to autoantibody against FVIII is rare with a biphasic age distribution in the elderly and in the post partum period. It is associated with autoimmune disorders, infections, and malignancy. Allo- or autoantibodies bind to coagulation factor and cause clearance by reticuloendothelial system or inhibit their functions, both of which result in bleeding tendency. These inhibitors are quantified and expressed as Bethesda units (BUs). A titer of <5 BU is considered low titer antibody. The incidence of antibodies against FV and prothrombin has increased with frequent use of topical bovine thrombin in fibrin glue. The bovine thrombin preparation is contaminated with bovine FII and FV, once exposed to these bovine factors, patients can make antibodies which in turn cross react with human factors causing their deficiencies. Other reasons for FV antibodies are streptomycin, cefotaxime, tacrolimus, and infections (such as tuberculosis and HIV). Patients with lupus anticoagulant occasionally have selective prothrombin deficiency due to an antibody against FII and severe deficiency presents with bleeding in a patient with a diagnosis of antiphospholipid syndrome. Acquired FX deficiency is frequently associated with systemic amyloidosis due to selective binding of FX to amyloid fibrils. Acquired von Willebrand's syndrome (AVWS) is frequently associated with autoimmune, hematologic or cardiovascular diseases.

Current management/treatment

In patients with factor inhibitors, the therapy should be individualized, depending on the clinical setting, presence or absence of bleeding, and the inhibitor titer. The goals of therapy include cessation of bleeding and suppression of inhibitor production. The current treatment options for bleeding include: high doses of FVIII for low titer inhibitor (<5 BU) and FVIII bypassing products for high titer inhibitors (>5 BU) that include activated prothrombin complex concentrates (FEIBA or Autoplex®) and recombinant factor VIIa (Novoseven®). The treatment options for suppression of inhibitor production include high dose corticosteroids, rituximab, cyclophosphamide, cyclosporine or high dose IVIG. The immunologic tolerance can be induced by daily infusions of high-dose FVIII. Extracorporeal therapy-immunoadsorption is preferred over TPE.

Rationale for therapeutic apheresis

For patients with inhibitor the extracorporeal removal of antibodies with immunoadsorption is more effective than plasma exchange. There are currently two immunoadsorption techniques used in practice (both unavailable in the USA), one of them is sepharose-bound staphylococcal protein A (SPA) (Immunosorba®, Fresenius, Germany) the other is sepharose-bound polyclonal sheep antibodies against human Ig (Ig-Therasorb®, Germany). Polyclonal sheep antibodies bind all classes of immunoglobulin, whereas, SPA binding of IgG subclasses 1, 2, 4 are stronger than IgG_3, IgM and IgA. Because antibodies against coagulation factors are mostly IgG_4, SPA immunoadsorption is more effective in removal of antibodies and improvement of the clinical condition. SPA can also interact with the immune system, which may result in immunomodulation. These effects include a decrease in activated monocytes and cytotoxic T cells, a change in T cell population, and a decrease in autoreactive T cell activity. Immunosorba® utilizes two columns; one regenerates immunoglobulins while the other is adsorbing them. Thus, this system can remove a large amount of IgG. The reduction in inhibitor titer is temporary. Post-procedure antibody titer may be elevated due to the re-equilibration of antibodies from extravascular to intravascular space.

FV deficiency due to an inhibitor is treated with corticosteroid and platelets rather than plasma transfusion. This is due to the fact that FV present in alpha granules of platelets is protected from the inhibitor and released at the site of injury. Hypoprothrombinemia associated with lupus anticoagulant is treated with prothrombin complex concentrate and corticosteroids. There are no data supporting any benefit of TPE in treating coagulation factor inhibitors. AVWS is treated with corticosteroids and FEIBA or rFVIIa.

Technical notes

To remove inhibitors, plasma flow rates are 35-40 mL/minute in Immunosorba®; a three plasma-volume treatment (10 L) requires 20-30 adsorption cycles. Anticoagulant should be used at the lowest amount possible.

Volume treated: 1 to 1.5 TPV TPE; 3 TPV IA	**Frequency:** TPE for inhibitors - daily
	IA for inhibitors – Immunosorba: daily
Replacement fluid: TPE: plasma; IA: none	

Duration and discontinuation/number of procedures:

For inhibitors, daily until antibody titer decreases and bleeding can be easily controlled with other therapeutic modalities.

References [140,208–213]

*As of November 6, 2009 insert dates using PubMed and the MeSH search terms coagulation factor deficiency, coagulation factor inhibitors, factor VIII inhibitors, immunoadsorption, plasmapheresis and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

CRYOGLOBULINEMIA

Incidence: 1-2% of patients with chronic hepatitis C, approximately 80% of patients with cryoglobulinemia have hepatitis C	Procedure	Recommendation	Category
	TPE	Grade 1B	I (severe/symptomatic)
	IA	Grade 2B	II (secondary to hepatitis C)

# of reported patients*: 100–300

	RCT	CT	CS	CR	Type of evidence
TPE	0	0	18 (195)	>50	Type II-3
IA	1 (17)	0	1 (4)	0	Type I

Description of the disease

Cryoglobulins are immunoglobulins that reversibly precipitate below body temperature. The aggregates of cryoglobulins can deposit on small vessels and cause damage by activating complement and recruiting leukocytes. This most likely occurs on the skin of lower extremities because of exposure to lower temperatures. The end-organ complications secondary to cryoglobulinemia range from none to severe. Cryoglobulinemia is associated with a wide variety of diseases including lymphoproliferative disorders, autoimmune disorders, and viral infections (e.g. hepatitis B and C). Mild symptoms include purpura, arthralgia, and mild sensory neuropathy.

Severe symptoms include glomerulonephritis, neuropathy, and systemic vasculits. Cryoglobulins are classified into three types: type I consist of monoclonal immunoglobulins, usually due to multiple myeloma (IgG) or Waldenström's macroglobulinemia (IgM), type II contain polyclonal IgG and monoclonal IgM rheumatoid factor usually due to hepatitis C infection, and type III contain polyclonal IgG and IgM usually due to inflammatory disorders, autoimmune disease, or hepatitis C infection. About 80% of individuals with mixed cryoglobulinemia (types II and III) have hepatitis C. The diagnosis of cryoglobulinemia is made by history, physical findings, low complement levels and detection and characterization of cryoglobulins (cryocrit).

Current management/treatment

Management is based on the severity of symptoms and treating the underlying disorder. There is no correlation between the severity of disease and cryocrit. Individuals with type I have a higher cryocrit than individuals with type II or III. Asymptomatic individuals do not require treatment of their cryoglobulinemia. Mild symptoms can be treated with cold avoidance and analgesics. More severe disease warrants the use of immunosuppressive therapy such as corticosteroids, cyclophosphamide, and rituximab (anti-CD20). Additionally, interferon and ribavirin are used for the treatment of cryoglobulinemia related to hepatitis C infection. When cryoglobulinemia is associated with severe clinical manifestations such as skin ulcerations, glomerulonephritis or neuropathy, plasma exchange (TPE) can be used as an adjunct to control the symptoms by directly removing the cryoglobulins.

Rationale for therapeutic apheresis

TPE removes cryoglobulins efficiently. It is used in all types of cryoglobulinemia for a wide variety of clinical manifestations. TPE has been most used in active moderate to severe cryoglobulinemia with renal impairment (membranoproliferative glomerulonephritis), neuropathy, vasculitis and/ or ulcerating purpura. TPE can be performed in conjunction with steroids or cytotoxic agents or alone. It has been used in both the short and long term management. Case series and case reports suggest 70-80% improvement with TPE. Double cascade filtration, which separates plasma out of whole blood in the first filter and removes high molecular weight proteins in the second filter (such as IgM), has also been used to treat cryoglobulinemia. Another apheresis modality used in this disease is cryofiltration or cryoglobulinapheresis, which cools the plasma in an extracorporeal circuit either continuously or in a 2 step procedure to remove cryoglobulins, the remaining plasma is warmed to body temperature prior to returning to the patient. There is a single randomized controlled trial with or without immunoadsorption of patients with cryoglobulinemia associated with hepatitis C who had not responded to previous conventional medications. The patients first received 12 weeks of medical therapy and then received another 12 weeks of medical therapy (immunosuppression + anti-virals) with or without immunoadsorption apheresis (immunoadsorption with dextran sulfate; Selsorb®, [dextran sulfate], 3 times a week, 45 ml/kg processed for 12 weeks or fewer if symptoms resolved). Statistically greater clinical improvement using a previous published scoring system which assigns points for each organ's involvement and reflects the severity of involvement was demonstrated with the use of IA (80% vs 33%).

Technical notes

It is prudent to warm the room, draw/return lines, and/or replacement fluid. There is a single case report of a patient receiving plasma exchange who developed acute oliguric renal failure due to infusion of cold plasma and precipitation of cryoglobulin within glomerular capillary loops. Other cases have reported cryoglobulin precipitation in the extracorpeal circuit.

Volume treated: 1 to 1.5 TPV	**Frequency:** every 1 to 3 days
Replacement fluid: albumin or plasma	

Duration and discontinuation/number of procedures

The reports use a variety of number of treatments and frequencies. For acute symptoms, performance of 3-8 procedures, and re-evaluation for clinical benefit should be considered. TPE may rapidly improve acute symptoms and serve as a bridging therapy prior to treating the underlying disease and reducing immunoglobulin production with immunosuppressive drugs. Weekly to monthly maintenance treatments may be indicated in patients who initially responded to TPE in order to prevent recurrent symptoms. Because the cryocrit is not a marker of disease activity, it should not be used as a criterion for initiating or discontinuing TPE.

References [104,214–220]

*As of November 6, 2009 using PubMed and the MeSH search terms cryoglobinemia and plasmapheresis, plasma exchange, and immunoadsorption for articles published in the English language. References of the identified articles were searched for additional cases and trials.

CUTANEOUS T CELL LYMPHOMA/MYCOSIS FUNGOIDES/SÉZARY SYNDROME

Incidence: 0.3-1 per 100,000/year	Procedure	Recommendation	Category
	ECP	Grade 1B	I (Erythrodermic)
	ECP	Grade 2C	III (Nonerythrodermic)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
Erythrodermic	1 (8)	4 (64)	27 (530)	1 (2)	Type I
Nonerythrodermic	1 (8)	2 (18)	11 (83)	0	Type I

Description of the disease

Mycosis fungoides (MF) and its leukemic variant, Sézary Syndrome (SS) are the most common types of Cutaneous T Cell Lymphoma (CTCL) whose pathogenesis remains elusive. MF has four clinical stages: I includes skin patches and plaques (IA; <10% body surface area involved; and IB; ≥10%); II has lymphadenopathy without pathological nodal infiltration (IIA) or with cutaneous tumors (IIB); III presents with generalized erythroderma; and IV has lymph node involvement (IVA) and visceral disease (IVB). Stages IA, IB and IIA are considered ''limited or early-stage'' disease, and stages IIB, III and IV are ''advanced-stage'' disease. Erythroderma, generalized lymphadenopathy and malignant T cells (Sézary cells) in skin, lymph nodes and peripheral blood characterize SS. Pruritus may be present in all stages and may be debilitating, demanding therapeutic intervention. Patients with advanced-stage disease without visceral involvement have a median survival of five years from time of diagnosis. The most common cause of death from CTCL is bacteremia from infected skin lesions.

Current management/treatment

MF and SS are incurable but indolent processes which therapies aim at improving symptoms and skin appearance. Limited-stage disease typically responds to topical measures (corticosteroids or chemotherapy, phototherapy (PUVA or UVB), bexarotene and radiotherapy). Patients with refractory limited- or advanced-stage disease require systemic measures such as retinoids (bexarotene), interferon-α, histone deacetylase inhibitors, the fusion toxin denileukin diftitox, systemic chemotherapy, ECP and/or hematopoietic stem cell transplantation. The concurrent use of multiple agents have yielded response rates of up to 80% with complete responses of 30% lasting for up to 1 year. In a limited number of patients, Wain et al suggested that methotrexate and ECP were similarly efficacious, although all patients who received both treatments preferred ECP due to fewer side-effects and the opportunity to meet other patients during the apheresis sessions.

Rationale for therapeutic apheresis

ECP was approved in 1987 based on the study by Edelson et al. Scarisbrick and colleagues have recently concluded that all patients with erythrodermic CTCL (major criteria) are candidates for ECP, specifically those with a peripheral blood T-cell clone and /or circulating Sézary cells comprising >10% of the lymphocytes and/or CD4 / CD8 ratio >10 (minor criteria). Response to ECP has been linked to short duration of disease, absence of bulky lymphadenopathy or internal organ involvement, white blood cell count <20,000/μL, <20% Sézary cells, normal or mildly abnormal natural killer cell activity, CD8+ T cells above 15%, lack of prior intensive chemotherapy and plaque-stage disease involving only 10-15% of the skin surface. Fewer patients with nonerythrodermic CTCL have been treated with ECP and the only randomized crossover study suggested no ECP benefit. However, among more than 100 patients with early-stage CTCL treated with ECP published thus far, response rates ranged from 33% to 88% for monotherapy or 50-60% when ECP was combined with adjuvant therapies. Several studies suggest that ECP prolongs survival of patients with advanced disease.

Technical notes

One to two cycles (two daily ECP procedures) per month have yielded comparable results to more intensive regimens. For patients with Sézary cell count > 1000/μL, twice monthly cycles have been suggested.

Volume treated: ECP: An MNC product of 200 - 270 mL. The two step process method collects and treats MNCs obtained from 2-times TBV processing.
Replacement fluid: NA

Frequency: Treatments on two consecutive days every 2 to 4 weeks

Duration and discontinuation/number of procedures

The median time for a response to ECP is 5–6 months although some patients take as long as 10 months. Those who respond after 6 to 8 cycles appear to have an improved long-term outcome. During ECP, patients should be monitored monthly to document skin changes and blood response (Sézary syndrome). If the cutaneous and the blood response are discrepant, the parameter showing the least improvement should be used to determine ECP effectiveness. Pruritus is assessed with a visual analogue scale score. Lymph node involvement is another indicator of treatment response. Since psychosocial disability is common in patients with advanced CTCL, response to ECP can be documented using a quality of life questionnaire. Initially, ECP should be planned for a minimum of 6 months. When maximal response is achieved, it can be reduced to once every 6–12 weeks with the goal of discontinuation if no relapses occur. If CTCL recurs in > 25% of the skin, ECP once or twice monthly should be reinstituted. If there is evidence of disease progression after 6 months of ECP alone, combination therapy should be considered. If there is minimal or no response after 3 months of combination therapy, ECP should be discontinued.

References [170,221–233]

*As of January 9, 2010 using Pub Med and journals published in the English language using the search terms cutaneous T-cell lymphoma, Sézary syndrome, extracorporeal photochemotherapy (ECP), and photopheresis. References of the identified articles were searched for additional cases and trials.

DILATED CARDIOMYOPATHY

Incidence: 36 per 100,000/year in the US			Procedure	Recommendation	Category
			IA	Grade 2B	III (NYHA II-IV)
			TPE	Grade 2C	III (NYHA II-IV)

# of reported patients*: >300					
	RCT	CT	CS	CR	Type of evidence
IA	3 (65)	6 (151)	10 (120)	1	Type I
TPE	0 (0)	0	1 (9)	2	Type II-3

Description of the disease

Dilated cardiomyopathy (DCM) is characterized by cardiac enlargement with impaired ventricular systolic function. While an uncommon cause of congestive heart failure it accounts for half of heart transplants in the US. The pathogenesis of DCM involves myocardial viral infection, inherited susceptibility factors, environmental variables, and immune variables. In 25% of patients with DCM, viral genome can be detected on endomyocardial biopsy and most have one or more cardiac autoantibodies.

Current management/treatment

DCM is treated with angiotensin converting inhibitors, angiotensin receptor blockers, diuretics, digitalis, β-blockers, aldosterone antagonists, and vitamin K antagonists. The definitive therapy is cardiac transplantation.

Rationale for therapeutic apheresis

Eighty percent of DCM patients have autoantibodies to myocardial antigens such as myosin heavy chain, β1-adrenergic receptor, mitochondrial antigens, adenosine diphosphate carrier protein, adenosine triphosphate carrier protein, M2 muscarinic receptor, and troponin I. These can cause lysis, decrease contractility, and impair calcium transport of isolated rat cardiomyocytes in bioassays. Rabbits immunized with β1-adrenergic receptor extracellular domain develop morphologic and clinical evidence of DCM. Treatment of DCM with immunosuppression and/or intravenous immunoglobulin (IVIG) have had mixed results. Treatment of acute myocarditis has not been successful.

Trials and case series using IA columns (i.e. sheep anti-human polyclonal antibody, Staphylococcal protein A agarose (SPAA), recombinant β1-adrenergic receptor extracellular domains, tryptophan polyvinyl alcohol) have demonstrated short- and long-term improvement as measured by echocardiography, invasive monitoring, standardized symptom assessments, and oxidative stress markers. Histologic improvements include decreased HLA expression, myocardial inflammation, and myocyte desmin gene expression. Improved function has been reported to last through the end of study follow-up, 3 to 12 months after treatment. One series found left ventricular ejection fraction (LVEF) improvement in 5 of 9 patients 3 years after a single course of IA. Most studies have examined patients with cardiac autoantibodies. One controlled trial examined the effects of IA on patients with cardiac depressant antibodies and those whose antibodies did not depress function. Only patients with depressant antibodies improved. One series found improvement in all patients treated, even those without cardiac autoantibodies.

Preliminary data from a series of 9 TPE treated patients has been published. Seven of 9 patients demonstrated improvement in LVEF, quality of life score, New York Heart Association (NYHA) functional class, and a decline in myocardial IgG deposition. Improvement in NYHA functional class persisted for 6 months. TPE has also been used in two patients with β1-adrenergic receptor antibodies due to the lack of available IA columns (one adult) and excessive extracorporeal volume of the IA device (one child). Cardiac function improved such that the adult was no longer eligible for cardiac transplantation. This persisted for 12 months when he demonstrated worsening echocardiograph findings. Repeat TPE course improved function. Dobutamine was weaned and diuretic dose was reduced in the pediatric patient following TPE. Improvement persisted for 3 months.

Technical notes

Studies have focused on patients with optimum medical management with chronic DCM, i.e. those with symptoms for ≥6 months. Treatment of acute DCM has not been examined. Trials have used sheep anti-human immunoglobulin columns or SPAA columns. Comparison of these found SPAA less effective due to a lower affinity for pathogenic IgG3 antibodies. Modified SPAA protocols can enhance IgG3 removal and have demonstrated efficacy. IVIG (0.5 g/kg) was given after last apheresis treatment in most IA studies and the TPE case series.

Volume treated: Not reported in most IA trials. One trial targeted 5 L.	**Frequency:** IA: Various schedules: 5 treatments on consecutive days; 3 treatments on consecutive days followed by two consecutive treatments a month for three months; 5 treatments on consecutive days repeated every month for four months.
TPE case: 1.5 TPV. Not reported for case series.	TPE: Five treatments on consecutive days.
Replacement fluid: IA: Not applicable TPE: albumin	

Duration and discontinuation/number of procedures

An IA trial comparing a single course of 5 consecutive days of treatment to the 5 consecutive days repeated every four weeks for 4 courses failed to demonstrate differences in LVEF at 3 and 6 months between the two treatment schemas. Repeat IA and TPE have been reported to be effective in patients experiencing worsening function.

References [234–250]

*As of October 11, 2009 using PubMed and the MeSH search terms dilated cardiomyopathy and plasma exchange or plasmapheresis or immunosorbent technique or immunosorbent or immunoadsorption for articles published in the English language. References of the identified articles were searched for additional cases and trials. This fact sheet includes abstracts in the summary of published reports and considers them in determining the recommendation grade and category.

FAMILIAL HYPERCHOLESTEROLEMIA

Incidence: Heterozygotes 200 per 100,000/year; Homozygotes 1 per 1,000,000/year	Procedure	Recommendation	Category
	Selective removal	Grade 1A	I (homozygotes)**
	Selective removal	Grade 1A	II (heterozygotes)
	TPE	Grade 1C	II (homozygotes with small blood volume)***

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
Selective removal	6 (228)	14 (277)	19 (306)	NA	Type I
TPE	0	1 (5)	14 (62)	NA	Type II-2

**approved indications vary among countries, See technical notes.

***relative to manufacturers' recommendation for available selective removal devices

Description of the disease

Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by mutations of hepatocyte apolipoprotein-B (apo-B) receptors that result in decreased hepatic LDL removal. FH exhibits gene dosage: Homozygotes exhibit cholesterol of 650–1,000 mg/dL, xanthomata by age 4 years, and death from coronary heart disease by age 20. Heterozygotes exhibit cholesterol of 250-550 mg/dL, xanthomata by age 20 years, and atherosclerosis by age 30.

Current management/treatment

HMG-CoA reductase inhibitors, bile acid binding resins, nicotinic acid, and dietary modification can significantly reduce cholesterol in heterozygotes, but homozygotes and some heterozygotes are unresponsive or intolerant to these. Last resort therapies include distal ileal bypass, portacaval shunting, and liver transplantation. TPE was first used in 1975 to reduce cholesterol but removal of beneficial substances prompted development of selective removal systems.

Rationale for therapeutic apheresis

A single treatment reduces LDL cholesterol levels 50–60%. Short-term effects include improved myocardial and peripheral blood flow as well as endothelial function. LDL apheresis also alters atherogenic LDL subclass distribution and decreases adhesion molecule expression (VCAM-1, E-selectin, and ICAM-1). Because of the slow rise in LDL and Lp(a) levels following treatment (1–2 weeks), the time-averaged cholesterol is reduced with repeated treatments. Long-term angiographic, ultrasound, and CT studies have demonstrated stabilization or regression of coronary stenoses, widening of coronary artery diameter, decrease in plaque area, and decrease in plaque calcification. Long-term outcome studies have demonstrated significant reductions in coronary events.

Technical notes

Six selective removal systems are available. These are: (1) immunoadsorption: columns containing matrix bound sheep anti-apo-B antibodies, (2) dextran sulfate columns: remove apo-B containing lipoproteins from plasma by electrostatic interaction, (3) heparin extracorporeal LDL precipitation (H.E.L.P.): precipitates apo-B molecules in the presence of heparin and low pH, (4) direct adsorption of lipoprotein using hemoperfusion: removes apo-B lipoproteins from whole blood through electrostatic interactions with polyacrylate coated polyacrlyaminde beads, (5) dextran sulfate cellulose columns: remove apo-B containing lipoproteins from whole blood through electrostatic interactions, and (6) membrane differential filtration: filters LDL from plasma. All have equivalent cholesterol reduction and side effects. Currently, the dextran sulfate plasma adsorption and H.E.L.P. systems are approved by the Food and Drug Administration (FDA).

Angiotensin converting enzyme (ACE) inhibitors are contraindicated in patients undergoing adsorption-based LDL apheresis. The columns function as a surface for plasma kallikrein generation which, in turn, converts bradykininogen to bradykinin. Kininase II inactivation of bradykinin is prevented by ACE inhibition resulting in unopposed bradykinin effect, hypotension and flushing. This is not seen with the H.E.L.P. system.

The goal is to reduce time-averaged total cholesterol 45–55%, LDL 40–60%, and Lp(a) 40–60%. Numerous patient treatment criteria have been published. FDA approved indications are: (1) functional homozygotes with LDL >500 mg/dL, (2) functional heterozygotes with no known cardiovascular disease but LDL ≥300 mg/dL, and (3) functional heterozygotes with known cardiovascular disease and LDL ≥200 mg/dL. The International Panel on Management of FH (Spain) indications are (1) FH homozygotes and (2) heterozygotes with symptomatic coronary artery disease in whom LDL is >4.2 mmol/L (162 mg/dL) or decreases by <40% despite maximal medical management. The German Federal Committee of Physicians and Health Insurance Funds criteria are: (1) FH homozygotes and (2) patients with severe hypercholesterolemia in whom maximal dietary and drug therapy for >1 year has failed to lower cholesterol sufficiently. The HEART-UK criteria are: (1) FH homozygotes in whom LDL is reduced by <50% and/or >9 mmol/L (348 mg/dL) with drug therapy, (2) FH heterozygotes or a ''bad family history'' with objective evidence of coronary disease progression and LDL >5.0 mmol/L (193 mg/dL) or decreases by <40% despite drug therapy, and (3) progressive coronary artery disease, severe hypercholesterolemia, and Lp(a) >60 mg/dL in whom LDL remains elevated despite drug therapy. Patients without FH but with very high LDL or Lp(a) unresponsive to or who cannot tolerate conventional therapy can also be treated. During pregnancy, LDL levels in individuals affected by FH can rise to extreme levels that can compromise uteroplacental perfusion. There have been case reports of the use of LDL apheresis to allow for the successful completion of pregnancy.

TPE can be effective the availability of the selective removal systems and their superior efficacy in cholesterol removal makes its use uncommon. TPE may be the only option in small children where the extracorporeal volume of selective removal systems is too large. It has been recommended that LDL apheresis begin by age 6 or 7 to prevent aortic stenosis that can occur in homozygous FH.

Volume treated: 1 to 1.5 TPV

Replacement fluid: selective removal: not applicable; TPE: albumin

Frequency: once every 1 to 2 weeks

Duration and discontinuation/number of procedures

Treatment is continued indefinitely, adjusted to maintain the time-averaged lipoprotein levels as described.

References [251–257]

*as of October 12, 2009 using PubMed and the MeSH search terms hypercholesterolemia and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS RECURRENT

Incidence: rare				Procedure	Recommendation	Category
				TPE	Grade 1C	I

# of reported patients*: 100-300

RCT	CT	CS	CR	Type of evidence
0	2 (19)	43 (117)	8 (10)	Type II-3

Description of the disease

Focal segmental glomerulosclerosis (FSGS) causes 15% to 20% of cases of nephrotic syndrome in children and adults. Instead of a specific diagnosis, FSGS is a histologically characteristic finding in renal biopsies characterized by focal areas of sclerosis of some glomeruli adjacent to other intact glomeruli. Several FSGS histological variants (cellular, collapsing, tip lesion, perihilar, nonsclerotic, and not otherwise specified) have been described. FSGS variants appear to have different clinical presentations and treatment response. Most patients with FSGS do not have underlying conditions, although FSGS may be associated with morbid obesity, vesicourethral reflux, heroin use or HIV infection, in addition to renal pathologies such as mutations in nephrin, lupus nephritis, vasculitis or IgA nephropathy. Idiopathic or primary FSGS is postulated to result from a plasma factor that increases glomerular permeability. This hypothesis is supported by the observation that FSGS may recur in a renal allograft. However, the presence of such a permeability factor has not been confirmed although some of its characteristics have been described. Another possibility to explain the pathogenesis of FSGS is lack of an inhibitor to the permeability factor. Hence, what causes FSGS and why it may recur in a transplanted kidney is yet unknown. Renal failure is expected in most patients with FSGS within 3 to 7 years, making transplantation a desirable option to avoid lifelong dialysis. Unfortunately, 20-30% of transplanted patients will experience a recurrence in the renal allograft, especially children. Clinical studies suggest that other risk factors for FSGS recurrence are severity of pre-transplant FSGS, bilateral native nephrectomy, and kidney from a living donor. There are conflicting results in terms of gender as a risk factor for recurrence. FSGS in the transplanted kidney is diagnosed histologically or when nephrotic range proteinuria develops in the post-operative period in patients with a history of FSGS in the native kidney or in a previous allograft. FSGS can also be suspected when patients with a history of FSGS have less severe but persistent proteinuria (>0.5 g/day) within the first 10 days post-transplant. If not treated, FSGS will ultimately lead to permanent graft loss within months. Those who lost grafts to recurrent FSGS have >80% chance of developing the same lesion in subsequently transplanted kidneys.

Current management/treatment

Patients with primary FSGS with proteinuria >3 g/day do not benefit from TPE and should be candidates for corticosteroids, which remain its mainstay of treatment. Recurrent FSGS usually responds to a combination of TPE, cyclosporine A, and/or an angiotensin II receptor antagonist (ARB) or an angiotensin-converting enzyme inhibitor (ACEI). More recently, rituximab and mycophenolate mofetil have also been used in conjunction with TPE. Although the optimum timing of initiating TPE has not been studied, it is suspected that TPE should be instituted as soon as recurrent FSGS is diagnosed in order to halt the process and maintain renal function.

Rationale for therapeutic apheresis

FSGS patients appear to have an ill-defined ''permeability factor'', probably a glycoprotein of molecular weight of 30-50 kDa capable of inducing profound leakage of albumin when incubated with isolated rat glomeruli. Such factor has been shown to be removed by TPE and its decreasing plasma concentration coincides with improvement in proteinuria. Rare patients have been reported that had prophylactic TPE pre-transplant in order to avoid recurrent FSGS in the allograft. Most commonly, TPE is started when the diagnosis is made. The number of treatments needed to control proteinuria, surrogate marker of FSGS, is quite variable and can reach dozens. Garcia et al treated 9 children with 10 TPE sessions plus high doses of cyclosporine, mycophenolate mofetil, and prednisone, starting <48 hours after the diagnosis of proteinuria and reported a 55% complete remission and 12% partial response rates compared with no remissions among 5 children who did not receive TPE. In a study of adults in France, 8 of 9 patients achieved partial or complete remission of proteinuria with TPE but 5 still lost their grafts due to FSGS relapse. The authors concluded that the benefit of TPE is transient, especially if given as the sole immunosuppression. Valdivia et al treated 7 adults with recurrent FSGS with 17 sessions of TPE exchanging a fixed volume of 2.5 liters and reported that all patients had functioning grafts at an average of 10 months of follow-up. Sener et al reported on 4 adults treated with 9-15 sessions of TPE and mycophenolate mofetil who had preserved renal function as late as 34 months after transplant. A recent retrospective study of adults with FSGS by Moroni and colleagues suggested that TPE and ACEIs resulted in either complete or partial remission of proteinuria in 80% of patients at the end of therapy. Some patients with recurrent FSGS have been treated with partial success with a combination of TPE and immunoadsorption with staphylococcal protein A columns.

Technical notes

Vascular access may be obtained through arteriovenous fistulas or grafts used for dialysis.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin or albumin/plasma	

Duration and discontinuation/number of procedures

One approach is to begin with 3 daily TPEs followed by at least 6 more TPEs in the subsequent 2 weeks, for a minimum of 9 procedures. Usually proteinuria decreases gradually while the patient is being treated with TPE as well as the creatinine, in those patients who showed decreased renal clearance at diagnosis of FSGS recurrence. Tapering should be decided on a case by case basis and is guided by the degree of proteinuria. Timing of clinical response is quite variable and complete abolishment of proteinuria may take several weeks to months. Some patients require long-term regimens of weekly to monthly TPEs to prevent reappearance of the proteinuria. There are no clinical or laboratory characteristics that predict the likelihood of success with TPE.

References [258–273]

*As of November 10, 2009 using PubMed and journals published in English language using the search terms FSGS, recurrent FSGS, plasmapheresis, and therapeutic plasma exchange (TPE). References of the identified articles were searched for additional cases and trials.

GRAFT-VERSUS-HOST DISEASE

Incidence after allogeneic HSCT:**	Procedure	Recommendation	Category
13%-63% Grade II–IV acute GVHD	ECP	Grade 1B	II skin (chronic)
6%-80% Moderate-severe chronic GVHD	ECP	Grade 2C	II skin (acute)
	ECP	Grade 2C	III non-skin (acute/chronic)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
Chronic skin GVHD	1 (95)	0	0	0	Type I
Acute/chronic skin and non-skin GVHD	0	2 (41)	37 (623)	9 (13)	Type II-2

Description of the disease

Graft-versus-host disease (GVHD) following allogeneic hematopoietic stem cell transplantation (HSCT) is classified as either acute (aGVHD), chronic (cGVHD) or an overlap syndrome. Classic aGVHD occurs at ≤100 days after HSCT and affects the skin, gastrointestinal (GI) tract and/or liver. ''Late-onset'' aGVHD occurs, recurs or persists at >100 days and consists of typical aGVHD without diagnostic features of cGVHD. Acute GVHD results from activation of donor T-cells by host antigen-presenting cells, leading to T cell- and cytokine-mediated tissue injury. The pathophysiology of chronic GVHD is unclear but likely relates to persistent donor allo- or autoreactive T cells, B cells and natural killer (NK) cells that cause fibrosis, inflammation, sclerosis and atrophy of skin, lacrimal glands, mouth, lungs, gastrointestinal tract, liver, joints and vagina. Detailed clinical assessment and severity scores have been developed to systematically grade aGVHD and cGVHD.

Current management/treatment

Acute GVHD of grades II to IV severity is treated with a calcineurin inhibitor, systemic corticosteroids and, for GI disease, oral nonabsorbable steroids. The roughly 50% of patients who do not completely respond will suffer steroid side effects, infections and progressive end-organ complications. Antithymocyte globulin, anti-T cell or anti-cytokine antibodies, mycophenolate mofetil, sirolimus, pentostatin, mesenchymal stromal cells and extracorporeal photopheresis (ECP) are used for salvage therapy. Moderate to severe cGVHD is also treated with systemic immunosuppressive agents, including calcineurin inhibitors, mycophenolate mofetil and sirolimus, plus high-dose corticosteroids and topical/local measures. Interventions for steroid refractory or dependent patients include azathioprine, pentostatin, monoclonal antibodies against T cells, B cells or cytokines and ECP. Persistent cGVHD leads to severe steroid side effects, opportunistic infections, permanent tissue injury/dysfunction and disability.

Rationale for therapeutic apheresis

ECP involves three steps: (1) collection of peripheral blood leukocytes by apheresis; (2) extracorporeal exposure of the leukocytes to 8-methoxypsoralen (8-MOP) followed by irradiation with ultraviolet A (UVA) light; and (3) reinfusion of the photoactivated cells. The therapeutic effect of ECP for GVHD appears to involve induction of apoptosis in treated lymphocytes, modulation of monocyte-derived dendritic cell (DC) differentiation, a switch from pro-inflammatory to anti-inflammatory cytokine production by T-helper cell populations and induction of regulatory T cells to eventually establish immune tolerance. A number of retrospective and prospective cohort studies using ECP for GVHD have been reported. Overall response rates for steroid-refractory aGVHD in pediatric and adult patients range from 52-100%; with responses in skin, GI tract and liver ranging from 66-100%, 40-83% and 27-71%, respectively. Complete responses outnumber partial responses. ECP usually fails to benefit patients with severe (grade IV) aGVHD. ECP induces responses in approximately two-thirds of steroid-dependent patients with cGVHD. Skin, oral and ocular manifestations improve in 40-100% and liver, joint and GI complications respond in roughly 30-80%, 50% and 0-50% of cases, respectively. Maximal responses often require 2 to 6 months of treatment and most are partial rather than complete. The single, randomized controlled trial using ECP for steroid-resistant cGVHD of the skin observed no statistically significant difference in total skin score at 12 weeks in patients receiving ECP plus salvage GVHD therapy (n=48) compared to salvage therapy alone (n=47). However, unblinded assessments recorded 40% complete and partial responses at 12 weeks in the ECP-treated group compared to 10% in the non-ECP group (p < 0.001) and more rapid skin improvement was observed during weeks 12 to 24 of ECP. In this trial and in many retrospective studies, ECP greatly facilitated a rapid corticosteroid taper, thereby reducing the risk of immunosuppressive complications. The British Photodermatology Group and the UK Skin Lymphoma Group published evidence-based practice guidelines on ECP in early 2006 (McKenna et al.); notably, the recommendations regarding GVHD were based on study data published only through 2001.

Technical notes

ECP in individuals ≥40 kg can be performed using an intermittent-flow system and 8-MOP approved for the treatment of cutaneous T cell lymphoma (the UVAR® XTS™ photopheresis system; Therakos Inc. Exton, PA, USA). A new instrument, the Cellex™ (Therakos), approved in early 2009 utilizes a continuous-flow system and can safely treat patients with body weight as low as 22 kg. With blood prime, the Cellex™ instrument can treat children weighing <25 kg. Heparin is the conventional anticoagulant for Therakos instruments but ACD-A can be substituted if necessary. An alternative two step process method is commonly used in Europe and for smaller body weight patients (i.e. weight <40 kg or when the extracorporeal volume exceeds 15% at any time during the collection or processing of the blood). This involves collecting mononuclear cells (MNC) by standard continuous-flow apheresis, photoactivating the MNC either by processing through the UVAR® XTS™ system or by using a UVA lightbox (not approved in the U.S.) and reinfusing the treated cells.

Volume treated: An MNC product of 200 - 270 mL. The two step process method collects and treats MNCs obtained from 2-times TBV processing.	**Frequency:** two consecutive days (one series) every one to two weeks
Replacement fluid: all photoactivated leukocytes are reinfused: albumin, saline	

Duration and discontinuation/number of procedures

For aGVHD, one series is performed weekly until disease response and then tapered to every-other-week before discontinuation. For cGVHD, one series weekly until either a response or for 8 to 12 weeks, followed by a taper to every 2 to 4 weeks until maximal response.

References [227,274–290]

*As of October 1, 2009 using PubMed and the MeSH search terms graft-versus-host disease, GVHD, extracorporeal photochemotherapy, ECP, photopheresis, for articles published in the English language. References of the identified articles were searched for additional cases and trials.
** Varies depending on age, conditioning regimen, graft source, graft manipulation and HLA matching.

HEREDITARY HEMOCHROMATOSIS

Incidence: 1.4 per 100,000/year				Procedure	Recommendation	Category
				Erythrocytapheresis	Grade 2B	III

# of reported patients*: 100-300

RCT	CT	CS	CR	Type of evidence
1 (38)**	0	11 (109)	0	Type II-3

**only preliminary data on 26 patients have been reported (as of 11/2009).

Description of the disease

This inherited disorder results in iron deposition in the liver, heart, pancreas and other organs. Its prevalence is approximately 1:200 among Caucasians. The genetic mutation, accounting for >90% of cases (and almost all cases in Caucasians of Northern European ancestry) is homozygosity for a single missense mutation in the HFE gene on chromosome 6p21 that results in substitution of cysteine with tyrosine at amino acid 282 and is referred to as the C282Y mutation. Abnormalities of the HFE gene may result in a defect in iron sensing in the deep crypt cells of gut epithelium and thus inappropriate iron uptake despite abundant iron stores in the body. Other mutations, in genes coding for hemojuvelin, hepcidin, transferrin receptors or ferroportin, have been described in families with syndromes of hereditary hemochromatosis. Iron accumulation in organs slowly results in liver failure (cirrhosis, hepatocellular carcinoma), diabetes, hypogonadism, hypopituitarism, arthropathy, cardiomyopathy and skin pigmentation. At diagnosis, the saturation of serum transferrin or iron binding capacity will be elevated ($\geq$45%) as will the serum ferritin ($\geq$300 ng/mL in men, $\geq$200 ng/mL in premenopausal woman), even in asymptomatic patients.

Current management/treatment

Because hereditary hemochromatosis is a disease of iron loading, iron removal by therapeutic phlebotomy is the mainstay of treatment. Phlebotomy therapy should be started in all patients whose serum ferritin level is elevated despite older age or the absence of symptoms. Typically, 1 unit of whole blood is removed weekly until the serum ferritin is <50 ng/mL without resultant anemia. Thereafter 2-4 phlebotomies per year are needed to maintain the ferritin $\leq$50 ng/mL. Malaise, weakness, fatigability and liver transaminase elevations often improve during the first several weeks of treatment, but joint symptoms may initially worsen before eventually improving (if at all). Cardiomyopathy and cardiac arrhythmias may resolve with phlebotomy, but insulin-dependent diabetes generally will not. The risk of hepatocellular carcinoma will persist if cirrhosis was present prior to the onset of phlebotomy therapy.

Rationale for therapeutic apheresis

Patients typically present with upward of 20 grams of excess iron thus, with 250 mg of iron removed per phlebotomy, two years may be needed to achieve therapeutic iron depletion. Each erythrocytapheresis removes two to three times that amount of red blood cells and iron while maintaining isovolemia. For example, in a prospective series of 13 patients the goal of each procedure was to remove a maximum of 800 ml of red cells and reduce the patient's hematocrit to 30%. Procedures were scheduled every 2-4 weeks to maintain the starting hematocrit $\geq$36%. Serum ferritin was reduced from (mean $\pm$ SD) 1517$\pm$1329 ng/mL to 20$\pm$6.5 ng/mL after 6.7$\pm$2.9 months and 13.5$\pm$7.2 apheresis sessions. A mean of 565.5$\pm$152 mL of red cells was removed with each procedure resulting in removal of 878$\pm$315 mg of iron per month. A prospective, randomized trial, under way in the Netherlands, compares erythrocytapheresis of 300-800 ml of erythrocytes every 2-3 weeks to a target hematocrit of $\geq$30% versus weekly phlebotomy of 500 ml of whole blood in 38 patients with newly diagnosed C282Y-positive hereditary hemochromatosis. Primary outcome measures are the duration and number of treatments to reach ferritin $\leq$50 ng/mL. Secondary outcome measures are decline in hemoglobin during treatment, improvement in liver function, patient discomfort and cost. Data from the first 26 study subjects have been published, and, not surprisingly, each erythrocytapheresis procedure removes more that twice the volume of erythrocytes of a phlebotomy procedure and 2.26-fold more iron. Whether erythrocytapheresis shortens the total treatment interval or is cost-effective versus phlebotomy remains to be determined. In a previous pilot study, published by the same group, 6 patients achieved iron depletion with erythrocytapheresis in (mean [range]) 9.8 [6-18] procedures over 4.8 [2-9] months versus 32 [22-48] procedures over 15.5 [10-24] months for 6 phlebotomy patients (historical controls).

Technical notes

While reported methods vary, the Dutch trial employs a schedule of erythrocytapheresis of 300-800 ml of erythrocytes every 2-3 weeks. The target hematocrit for each procedure is $\geq$30% and the threshold hematocrit for performing a procedure is 34%. The actual volume of erythrocytes to be removed (VR) with each procedure can be calculated as:

$$VR = [(\text{starting HCT} - \text{target HCT}) \div 79] \times \text{blood volume ml/kg} \times \text{body weight (kg)}].$$

Volume treated: Erythrocytapheresis of up to 800 ml of erythrocytes

Replacement fluid: Replace at least 1/2 to 1/3 of removed erythrocyte volume with saline.

Frequency: Every 2-3 weeks to keep post-procedure HCT $\geq$30%

Duration and discontinuation/number of procedures:

Erythrocytapheresis every 2-3 weeks, or as tolerated, until serum ferritin <50 ng/mL. Maintenance treatment can follow with infrequent therapeutic phlebotomy or erythrocytapheresis.

References [291–300]

*As of August 27, 2009 using PubMed and the MeSH search terms hemochromatosis and apheresis for journals published in the English language. References of the identified articles were searched for additional cases and trials.

HEMOLYTIC UREMIC SYNDROME

Incidence:	Procedure	Recommendation	Category
Diarrhea-associated HUS: 6.1/100,000 children under 5 years (overall incidence: 1–2/100,000)	TPE	Grade 2C	II (aHUS due to complement factor gene mutations)
Prevalence of Atypical HUS: 3.3 per 1,000,000 in those <18 y.o.	TPE	Grade 2C	I (aHUS due to autoantibody to factor H)
	TPE	Grade 1C	IV (d+HUS or typical HUS)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
aHUS due to complement factor gene mutations	0	0	2 (6)	20 (25)	Type III
aHUS due to autoantibody to factor H	0	0	2 (6)	2 (2)	Type III
d+HUS or typical HUS	0	0	4 (48)	4 (4)	Type II-3

Description of the disease

Hemolytic uremic syndrome (HUS), a thrombotic microangiopathy (TMA), comprises the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. The revised classification of TMA based on causation by the European Paediatric Research Group for HUS (referred as European Group) defines two subgroups of TMA: (1) that identified by well-defined etiology and (2) that recognized by a clinical association without clear etiology. The first subgroup includes HUS due to infection or complement dysregulation, TTP due to congenital or acquired ADAMTS13 deficiency and TMA secondary to defective cobalamine metabolism or quinine. The second subgroup includes TMA associated with disorders such as HIV, malignancy, chemotherapy, ionizing radiation, calcineurin inhibitors, hematopoietic progenitor cell or solid organ transplantation, pregnancy, SLE, antiphospholipid antibody syndrome, glomerular disorders, etc. Only HUS is discussed here.

Of infection-induced HUS, the most common form, which is called diarrhea-associated HUS (d+HUS) or typical HUS. d+HUS occurs 2-10 days after abrupt onset of bloody diarrhea due to verocytotoxin (Shiga-like toxin)-producing bacteria, predominantly Escherichia coli O157:H7. It accounts for 85-90% of all HUS, occurs primarily in children >6 months, can affect all ages, and has a favorable outcome with a mortality rate of <5%. The other infection-induced HUS that usually occurs in children <2 y.o. is due to sepsis, pneumonia, or meningitis caused by *Streptococus pneumoniae*. It has a mortality of 25% (19-50%). *S. pneumoniae* as well as other bacteria and viruses produce a neuramidase which cleaves sialic acid residues from cell surface glycoprotein exposing the Thomsen-Freidenreich (T-) antigen. HUS may occur by binding of naturally-occurring IgM anti-T antibody to exposed T-antigen on erythrocytes, platelets and endothelium.

The less common form of HUS occurs without diarrhea and is called d-HUS or atypical HUS (aHUS), accounting for 10% of cases. Approximately 60% of patients with aHUS have mutations and polymorphisms in the genes encoding both complement regulators [factor H (*CFH*), membrane cofactor protein (*MCP*), and factor I (*CFI*)] and complement activators [factor B (*CFB*) and *C3*]. *CFH* mutations are the most frequent (20-30%). Five percent of aHUS is due to thrombomodulin mutations causing defective complement regulation. Acquired complement dysregulation has been reported in 6-10% of aHUS cases due to anti-*CFH* autoantibodies. Infection, pregnancy or drugs may trigger clinical disease in the presence of these mutations. aHUS may present with an insidious onset at any age but many cases present in the first few months of life and is characterized by marked hypertension, frequent relapses, end stage renal disease (ESRD), and a mortality rate of 25%. Direct insult to microvasculature endothelial cells is the hypothetical mechanism of aHUS. Shiga toxin have proinflammatory and prothrombotic effects on the vascular endothelium and may attach to and stimulate endothelial cells to release ''unusually large'' von Willebrand factor (UL-vWf) multimers which activate and promote adhesion and aggregation of platelets. In familial aHUS, the lack of functional complement factors results in excessive activation of the alternate complement pathway causing glomerular injury. With the exception of infection-induced HUS, all children with HUS should be evaluated by measurement of *CFH, CFI, CFB, MCP, C3* and anti-*CFH* and genetic testing. All candidates for renal transplantation must have genetic testing, as transplantation outcome may be related to mutation type. The HUS recurrence rates on renal allografts are 80%, 100%, and 10% with *CFH, CFI* and *MCP* mutations, respectively. In addition, determination of ADAMTS13 activity is indicated to differentiate aHUS from TTP.

Current management/treatment

In children with infection induced-HUS, supportive care is the mainstay of therapy. Corticosteroids, plasma infusion or TPE have no proven role in d+HUS whereas some children with severe *S. pneumoniae*-induced HUS may benefit from TPE. In aHUS, plasma infusion can be initiated with 60-65mL of FFP/kg/week followed by 20 mL of FFP/kg/week as maintenance therapy. The European Group, based on expert consensus, recommends that TPE is initiated urgently as it may be more effective than plasma infusion and up to 25% of children progress to ESRD in their first episode. Hematological remission is defined as a platelet count $>150\times10^9$/L for 2 weeks with no signs of hemolysis (no fragmented red cells, elevated LDH). Rituximab may be initiated in aHUS due to anti-*CFH* autoantibodies. Overall, 50-60% of patients with aHUS progress to ESRD requiring dialysis, some eventually undergo renal transplantation. However, 30-100% of transplant patients, depending on the type of mutation, have recurrence in the graft, causing graft failure. The exception is the MCP mutations which is associated with favorable graft outcome. Since *CFH* and *CFI* are mostly hepatic in origin, liver or combined liver/kidney transplant have been tried. The alternative therapies may include use of purified complement factors or complement inhibitors, i.e., eculizumab.

Rationale for therapeutic apheresis

The rationale is that TPE can effectively remove the autoantibody or mutated circulating complement regulators while replacing absent or defective complement regulators. Despite conflicting reports of the effectiveness, the European Group as well as others recommend TPE over plasma infusion because of potential therapeutic benefits of TPE without a risk of volume overload or hyperproteinemia.

Technical notes

Since the majority of affected patients with aHUS are children, establishment of vascular access, red cell prime and calcium supplementation are of special concern. When TPE is performed in children with *S. pneumoniae*-induced HUS, avoidance of plasma-containing blood components is recommended to prevent the passive transfer of anti-T in normal plasma and possible polyagglutination due to T-activation.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily
Replacement fluid: plasma or albumin (T activation associated HUS)	

Duration and discontinuation/number of procedures

As there is no standardized approach, the duration and schedule of TPE for treatment of TTP have been empirically adopted to treat aHUS. European Group recommends that TPE be performed daily for 5 days after urgent initiation of TPE, 5 times per week for 2 weeks, then 3 times per week for 2 weeks with outcome evaluated at day 33. These guidelines address neither continued treatment after initial therapy failure nor ongoing prophylactic treatment for patients with remission. As shown in a recent case series of 3 patients with *CFH* mutation, acute and prophylactic TPE in the pre- and post-renal transplant periods were effective in maintaining long-term native and allograft kidney function. Decisions of duration or to discontinue should be made based upon patient response and condition.

References [301–321]

*As of January 31, 2010 using PubMed and the MeSH search terms hemolytic uremic syndrome, atypical hemolytic uremic syndrome, plasmapheresis, and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

HYPERLEUKOCYTOSIS

Incidence of hyperleukocytosis at diagnosis	Procedure	Recommendation	Category
AML, WBC >100 × 10⁹/L: ≤18%	Leukocytapheresis	Grade 1B	I (leukostasis)
ALL, WBC >400 × 10⁹/L: ≤3%	Leukocytapheresis	Grade 2C	III (prophylaxis)

# of reported patients*: > 300

	RCT	CT	CS	CR	Type of evidence
Acute myeloid leukemia	0	5 (385)	6 (184)	7 (9)	Type II-2
Acute lymphoblastic leukemia	0	3 (366)	3 (39)	NR	Type II-2

Description of the disease

Hyperleukocytosis is conventionally defined as a circulating white blood cell (WBC) or leukemic blast cell count >100 × 10⁹/L. Leukostasis complications of hyperleukocytosis include organ or tissue dysfunctions attributable to the high burden of circulating leukemic myeloid or lymphoid blast cells in the absence of infection, thromboembolism or other underlying etiology. In acute myeloid leukemia (AML), leukostasis complications usually occur when the WBC is >100 × 10⁹/L and in acute lymphoblastic leukemia (ALL) when the WBC is >400 × 10⁹/L. Patients with AML and an initial WBC count >100 × 10⁹/L have a 2- to 3-fold higher early mortality rate, primarily because of leukostasis complications and bleeding. Myeloid blasts are larger and more rigid than lymphoid blasts, and their cytokine products may upregulate endothelial cell adhesion molecule expression and activate inflammation. These processes can lead to microvascular leukoaggregates, hyperviscosity, tissue ischemia, infarction and hemorrhage. Clinical manifestations are not reliably predicted by the degree of hyperleukocytosis alone. A scoring system to grade the probability that end-organ manifestations with acute myeloid leukemia (AML) are due to leukostasis has been proposed. One study showed an association with early death and high lactate dehydrogenase (LDH), age >70 years, renal dysfunction or hyperbilirubinemia. The frequency and severity of leukostasis complications, particularly pulmonary, are greater with the monoblastic/monocytic subtypes (i.e. M4 and M5 AML), and are reported at blast counts <50 × 10⁹/L. Central nervous system (CNS) manifestations include confusion, somnolence, dizziness, headache, delirium, coma, and parenchymal hemorrhage with focal neurological deficits. Pulmonary complications include dyspnea, hypoxemia, diffuse alveolar hemorrhage, respiratory failure and radiographic findings of interstitial and/or alveolar infiltrates. Leukostasis complications have been reported in rare patients with chronic myelomonocytic leukemia with WBC counts >100 × 10⁹/L and high LDH concentration, and priapism may occur in patients with chronic myeloid leukemia and WBC counts >500 × 10⁹/L.

Current management/treatment

Definitive treatment of hyperleukocytosis in AML or ALL is with induction chemotherapy. Hydroxyurea or cytarabine are useful temporizing cytoreductive agents for AML. Tumor lysis syndrome and hyperuricemia, more common with ALL, are treated with intravenous fluids, electrolyte replacement, allopurinol or rasburicase, alkalinization of the urine and dialysis. Plasma, cryoprecipitate and/or platelets are given, as indicated, for bleeding or coagulopathy. Red cell transfusions should be avoided in patients with symptomatic leukostasis prior to cytoreduction because of the risk of augmenting hyperviscosity. Adjunctive radiation therapy may be considered in cases with parenchymal brain lesions; prophylactic cranial irradiation is not indicated.

Rationale for therapeutic apheresis

Multiple retrospective cohort studies in AML with hyperleukocytosis suggest that prophylactic leukocytapheresis can reduce the chance of early death (i.e. at ≤3 weeks into treatment) but later mortality and overall or long-term survival are not impacted. One cohort study showed that a post-leukocytapheresis WBC count of around 90 × 10⁹/L was not predictive of survival at one-week, suggesting that a lower therapeutic endpoint is necessary and/or that associated comorbidities are more important determinants of outcome. A second cohort study found no decrease in early mortality and raised concerns that leukocytapheresis may delay the start of chemotherapy. Despite the inability to accurately predict leukostasis complications, prophylactic leukocytapheresis should be considered for AML patients with a blast count >100 × 10⁹/L, especially with a monocytic/monoblastic subtype, and should not delay induction chemotherapy. Among children and adults with ALL, clinical symptoms of leukostasis occur in <10% of those with WBC counts <400 × 10⁹/L. Prophylactic leukocytapheresis offers no advantage over aggressive induction chemotherapy and supportive care, including those with tumor lysis syndrome. By comparison, pulmonary and CNS complications develop in over 50% of children with ALL and a WBC count ≥400 × 10⁹/L. Prophylactic leukocytapheresis should, therefore, be considered in those patients. For patients with symptomatic leukostasis, a number of uncontrolled studies report that rapid cytoreduction with leukocytapheresis can improve pulmonary and CNS manifestations with either AML or ALL. Severe end-organ injury or hemorrhage may not improve, however, particularly if extensive pre-existing tissue damage exists. Leukocytapheresis should be repeated in persistently symptomatic patients until clinical manifestations resolve or a maximum benefit is achieved. Chemotherapy should not be postponed and is required to prevent rapid reaccumulation of circulating blasts.

Technical notes

A single leukocytapheresis can reduce the WBC count by 30% to 60%. The collect rate at the start and during the procedure should be adjusted and monitored to optimize WBC removal. Erythrocyte sedimenting agents (e.g. hydroxyethyl starch) are not required. Red cell priming may be employed for selected adults with severe anemia; however, undiluted packed red blood cells should be avoided in small children with hyperviscosity.

Volume treated: 1.5 to 2 TBV	**Frequency:** daily; twice-daily for life-threatening cases
Replacement fluid: crystalloid; albumin; plasma	

Duration and discontinuation/number of procedures

For prophylaxis of asymptomatic AML patients, discontinue when the blast cell count is <100 × 10⁹/L (monitor patients with monocytic subtypes often). For AML patients with leukostasis complications, discontinue when the blast cell count is <50 to 100 × 10⁹/L and clinical manifestations are resolved. For prophylaxis of asymptomatic ALL patients, discontinue treatment when the blast cell count is <400 × 10⁹/L; and for those with leukostasis complications, when the blast cell count is <400 × 10⁹/L and the clinical manifestations have resolved.

References [322–339]

*as October 1, 2009 using PubMed and the MeSH search terms hyperleukocytosis, leukostasis, apheresis, leukapheresis, leukocytapheresis and acute leukemia for reports published in the English language. References of the identified articles were searched for additional cases and trials.

HYPERTRIGLYCERIDEMIC PANCREATITIS

Incidence: 18 per 100,000/year				Procedure	Recommendation	Category
				TPE	Grade 2C	III

# of reported patients*:100-300					
RCT	CT	CS	CR	Type of evidence	
0	1 (29)	12 (132)	28	Type II-1	

Description of the disease

Hypertriglyceridemia (HTG) results from elevations in the lipoproteins responsible for triglyceride (TG) transport. Primary causes include mutations in genes such as those encoding lipoprotein lipase (LPL) and its activator apo C-II. Secondary causes include diabetes mellitus (DM), hypothyroidism, pregnancy, and medications. Extreme TG elevations are seen in homozygotes due to mutations as well as when secondary causes are superimposed upon underlying genetic defects. Complications occur when TG levels are >2,000 mg/dL. These include acute pancreatitis, chronic abdominal pain, hepatosplenomegaly, eruptive xanthomas, lipemia retinalis, peripheral neuropathy, memory loss/dementia, and dyspnea. Endothelial damage due to chemical irritation by fatty acids and lysolecithin is felt to cause pancreatitis while hyperviscosity and tissue deposition produce the other complications.

Lipoatrophy is a rare case of HTG, which is characterized by adipose tissue loss, diabetes mellitus, and HTG. HTG leads to organomegaly, pancreatitis, and rarely cutaneous xanthomas. The cause of this disorder is unknown.

Current management/treatment

Treatment includes dietary restriction and lipid lowering agent administration (e.g., fibrates and nicotinic acid derivatives). With acute pancreatitis due to HTG, additional treatments include total parenteral nutrition (TPN), complete avoidance of oral intake, and moderate caloric restriction. If DM is present, insulin is also administered. Heparin has also been administered as it releases LPL from endothelial stores enhancing TG clearance. Heparin may exacerbate hemorrhage into the pancreatic bed in the setting of pancreatitis and, therefore, its use is controversial.

Rationale for therapeutic apheresis

Reports, series, and a single nonrandomized controlled trial have examined the use of TPE to treat acute pancreatitis due to HTG. Reductions in TG levels of 46–80% have been reported with improvement in symptoms of pancreatitis following one to three TPE procedures. The single trial, however, found no difference between standard therapy (ST) and TPE (n=10) versus ST alone (n=19) with regard to mortality, systemic complications, and local complications in patients with severe pancreatitis. Adequate information was not provided to ascertain the comparability of the two groups. While the authors felt that these negative findings were due to delayed initiation of TPE and recommended earlier intervention, the time from diagnosis to start of TPE was not provided.

Eight case reports examined TPE use in pregnant women with HTG-induced pancreatitis. In six cases, TPE was performed due to the presence of pancreatitis. The number of treatments ranged from 1 to 10 (median 2) with Cesarean section due to fetal distress and delivery of a preterm infant occurring in 5 of 6 cases. In two additional cases, patients were treated prophylactically because of a history of pancreatitis. TPE was performed 6 and 13 times beginning at 25 and 19 weeks gestation, respectively. In both cases, healthy infants were delivered at 34 weeks. In one of these cases, treatment was determined by TG levels with a goal to maintain a TG below 1,000 mg/dl.

Two case reports have examined TPE in generalized lipoatrophy. Serial TPE was used to control HTG and avoid pancreatitis. One report found benefit while one did not. In the latter, a variety of metabolic abnormalities were noted following TPE, including amenorrhea, galactorrhea, proliferative retinopathy, and hypertension, that were attributed to the treatment and TPE was not recommended because of this. It should be noted that these have not been reported as complications of TPE and are therefore of questionable association.

Other causes of HTG pancreatitis which have been reported to be treated by TPE include HTG due to medications such as isotretinoin, ritonavir, cyclosporine, and asparaginase as well as case report of lipid emulsion over-dose in a patient on TPN. In all of these cases, treatment has been reported to be beneficial.

Two series have reported chronic TPE treatment in a total of 8 patients with recurring pancreatitis. Both series reported TPE reduced or prevented further episodes of pancreatitis. In the larger of the series (6 patients), the frequency of pancreatitis was reduced by 67%. Treatments were done at a frequency to maintain the TG levels below 150 mg/dL.

Technical notes

Both centrifugal and double membrane filtration TPE have been used to treat pancreatitis due to HTG. A comparison of these two methods found greater removal with centrifugal methods because of the tendency of the TG to clog the pores of the filters.

Reports have suggested that heparin be used as the anticoagulant for these procedures because of its ability to release LPL which should enhance TG reduction. Many reports have used ACD-A with similar TG reductions. Most reports have used albumin as the replacement fluid. Some have used plasma as it contains LPL and could enhance TG removal. No direct comparisons of anticoagulants or replacement fluids have been reported. Treatment has usually been implemented early in the course of the pancreatitis secondary to HTG though some authors have recommended its use only if there is no improvement with standard therapy.

Volume treated: 1 to 1.5 TPV	**Frequency:** Therapeutic: daily for one to three days depending upon patient course
	Prophylactic: every 2 to 4 weeks to maintain TG level below 150 mg/dL
Replacement fluid: albumin; plasma	

Duration and discontinuation/number of procedures

For patients with acute pancreatitis, one TPE has been sufficient to improve the patient's clinical condition and lower their TG levels with additional treatments if necessary. For patients treated prophylactically, chronic therapy for years has been reported.

References [340–348]

*As of January 4, 2010 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and hypertriglyceridemia and pancreatitis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

HYPERVISCOSITY IN MONOCLONAL GAMMOPATHIES

Incidence: 0.1-0.3 per 100,000/year	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 1B	I** (treatment of symptoms)
	TPE	Grade 1C	I** (prophylaxis for rituximab)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
treatment of symptoms	0	3 (46)	18 (253)	12 (12)	Type II-1
prophylaxis for rituximab	0	0 (0)	3 (45)	2 (2)	Type II-3

Description of the disease

Whole blood viscosity varies as a function of hematocrit, red blood cell aggregation, plasma proteins, and interactions between the blood and the blood vessel wall. As blood viscosity rises, a nonlinear increase in shear stress in small blood vessels, particularly at low initial shear rates, produces damage to fragile venular endothelium of the eye and other mucosal surfaces. The term ''hyperviscosity syndrome'' refers to the clinical sequelae of mucous membrane bleeding, retinopathy, and neurological impairment. Specific signs and symptoms include headache, dizziness, vertigo, nystagmus, hearing loss, visual impairment, somnolence, coma, and seizures. Other manifestations include congestive heart failure (related to plasma volume overexpansion), respiratory compromise, coagulation abnormalities, anemia, fatigue (perhaps related to anemia), peripheral polyneuropathy (depending on specific properties of the immunoglobulin), and anorexia. This syndrome occurs most typically in Waldenström's macroglobulinemia, a lymphoplasmacytic lymphoma associated with the elaboration of ≥3 g/dL of monoclonal IgM immunoglobulin (M-protein) in the plasma. It also occurs in multiple myeloma, a plasma cell dyscrasia, when there is ≥6–7 g/dL of monoclonal IgA or ≥4 g/dL of monoclonal IgG3 in the plasma. In vivo whole blood viscosity is not necessarily identical to in vitro serum viscosity (relative to water: normal range being 1.4–1.8 centipoise [cp]). Therefore, serum viscosity measurement does not consistently correlate with clinical symptoms among individual patients. Almost all patients will be symptomatic when their serum viscosity rises to between 6 and 7 cp. Some may be symptomatic at a viscosity as low as 3–4 cp, others not until their viscosity reaches 8–10 cp. Recent data indicate that early manifestations of hyperviscosity-related retinopathy in Waldenström's macroglobulinemia can be detected in the peripheral retina at a serum viscosity as low as 2.1 cp and IgM levels below 3 g/dL, using indirect opthalmoscopy. Finally, the tendency of many hospitals to outsource serum viscosity to reference laboratories renders this test potentially less useful than it once was due to uncertainties related to specimen integrity while in transit and to turnaround time.

Current management/treatment

Plasma removal has been successfully employed in the treatment of hyperviscosity syndrome in Waldenström's macroglobulinemia since 1959. Manual plasmapheresis techniques have been supplanted by automated plasma exchange. Because Waldenström's macroglobulinemia and multiple myeloma are lymphoproliferative disorders, they are not curable by plasma exchange alone. Alkylating agents, corticosteroids, targeted therapies and transplant approaches are used to affect long-term clinical control of the disease.

Rationale for therapeutic apheresis

Early reports demonstrated that manual removal of up to 8 units of plasma per day (8 liters in the first 1-2 weeks) could relieve symptoms of acute hyperviscosity syndrome, and that lowered viscosity could be maintained by a maintenance schedule of 2-4 units of plasma removed weekly. Today, removal of 8 liters of plasma can be accomplished in two consecutive daily treatments using automated equipment. As the M-protein level rises in the blood, its effect on viscosity increases logarithmically. At some point an individual patient reaches his/her symptomatic threshold. By the same token, at the symptomatic threshold, a relatively modest removal of M-protein from the plasma (by plasma exchange) will have a logarithmic viscosity-lowering effect. Thus plasma exchange is both rapid and efficient in relieving hyperviscosity. Plasma viscosity is a major determinant of capillary blood flow. Plasma exchange dramatically increases capillary blood flow, measured by video microscopy, after a single procedure. The incorporation of the anti-CD20 monoclonal antibody, rituximab, into common treatment regimens for Waldenström's macroglobulinemia presents another rationale for TPE in management of this disorder. Upward of half of patients receiving rituximab will experience an increase (''flare'') in IgM of ≥25% compared to their pre-treatment level within 4 weeks of initiation of rituximab treatment. Those with IgM ≥5000 mg/dl at the time of initiation of rituximab therapy are at particular risk for symptomatic hyperviscosity should the flare occur. Prophylactic plasma exchange is recommended for these patients. Careful monitoring of viscosity and IgM levels are recommended during treatment to determine if subsequent TPE are necessary.

Technical notes

There is no uniform consensus regarding the preferred exchange volume for treatment of hyperviscosity. It is understood that viscosity falls rapidly as M-protein is removed, thus relatively small exchange volumes are effective. Conventional calculations of plasma volume based on weight and hematocrit are inaccurate in M-protein disorders because of the expansion of plasma volume that is known to occur. Therefore an empirical exchange of 1 to 1.5 calculated plasma volumes per procedure seems reasonable. A direct comparison trial demonstrated that centrifugation apheresis is more efficient than cascade filtration in removing M-protein. Cascade filtration and membrane filtration techniques have been described in case reports, but most American institutions employ continuous centrifugation plasma exchange.

Volume treated: 1 to 1.5 calculated plasma volume	**Frequency:** daily
Replacement fluid: albumin or albumin/saline	

Duration and discontinuation/number of procedures

Patients can be treated daily until acute symptoms abate (generally 1-3 TPEs). At that point, serum viscosity measurement can be repeated to determine the patient's symptomatic viscosity threshold. Retinal changes in otherwise asymptomatic patients with Waldenström's macroglobulinemia respond dramatically to a single plasma exchange with marked or complete reversal of the abnormal findings. An empirical maintenance schedule of 1 plasma volume exchange every 1-4 weeks based on clinical symptoms may be employed to maintain clinical stability pending a salutary effect of medical therapy (e.g. chemotherapy, targeted therapy, etc.). Prophylactic TPE to lower IgM to <5000 mg/dl may be performed in preparation for a treatment regimen that includes rituximab.

References [349–366]

* As of September 5, 2009 using PubMed and the MeSH search terms hyperviscosity, Waldenström's macroglobulinemia, myeloma and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
** **Comments:** Despite the absence of Type I evidence to support the use of plasma exchange or plasmapheresis in the treatment of hyperviscosity syndrome, there have been accumulated more than 40 years of reports and case series with consistently positive results.

IMMUNE COMPLEX RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Incidence: 0.7 per 100,000/year		Procedure	Recommendation	Category
		TPE	Grade 2B	III

# of reported patients*: >300					
RCT	**CT**	**CS**	**CR**	**Type of evidence**	
7 (196)	0	21 (295)	NA	Type I**	

**Case series and trials have not distinguished between the various causes of RPGN making results difficult to interpret. Trials have included immune-complex RPGN as well as ANCA-associated RPGN, which is discussed in a separate fact sheet.

Description of the disease

Immune complex glomerulonephritis is one cause of the clinicopathologic entity, rapidly progressive glomerulonephritis (RPGN). RPGN consists of rapid loss of renal function with the histologic finding of crescent formation in over 50% of glomeruli. These crescents represent a proliferation of cells within Bowman's space of the glomerulus due to the extravasation of proteins into this space. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes.

RPGN is NOT A SINGLE DIEASE ENTITY but is a clinical syndrome that can result from a number of etiologies. RPGN is divided into three categories based on the immunoflourescence pattern on renal biopsy. These categories are:

1. Linear deposits of IgG due to autoantibodies to type IV collagen representing anti-glomerular basement membrane GN (anti-GBM). It accounts for 15% of cases. (See fact sheet on anti-glomerular basement antibody disease)

2. Granular deposits of immune complexes caused by a variety of GNs including post-streptococcal GN, Henoch-Schönlein purpura, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis. Immune-complex RPGN accounts for 24% of cases of RPGN.

3. Minimal immune deposits in the glomerulus with the presence of anti-neutrophil antibodies (either C-ANCA or P-ANCA) in the serum. This pauci-immune RPGN, also referred to as ANCA-associated RPGN, is seen in Wegener's granulomatosis (WG) and microscopic polyangiitis (MP) and accounts for 60% of RPGN cases (See fact sheet on ANCA-associated RPGN).

It is important for apheresis medicine practitioners to identify the specific category of RPGN present in their patient as TPE treatment protocols and responses differ among the three categories.

Current management/treatment

Therapy consists of administration of high-dose corticosteroid (e.g., methylprednisolone) and cytotoxic immunosuppressive drug (e.g., cyclophosphamide or azathioprine). Other drugs that have been used include leflunomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors, and antibodies against T-cells.

Rationale for therapeutic apheresis

Because of the benefit of TPE in anti-GBM, it was applied to all causes of RPGN. While early trials and series included all causes of RPGN, subsequent trials have excluded anti-GBM. The role of TPE has been examined in seven trials which include both pauci-immune (ANCA-associated RPGN) and immune-complex RPGN. There are NO trials of TPE for only immune-complex RPGN. In three out of seven trials that included a mixture of immune-complex RPGN and pauci-immune RPGN, there was no benefit of TPE over standard therapy. Two trials that included immune-complex RPGN and pauci-immune RPGN showed benefit in patients who were dialysis dependent at the time of presentation and no benefit to those who had mild disease. In two small trials (14 and 15 patients) with a mixture of immune-complex and pauci-immune RPGN, benefit was seen in all patients. In a review of these trials in the Cochrane Database, the data were interpreted to suggest that TPE may be beneficial for dialysis-dependent patients presenting with severe renal dysfunction; however, there is no therapeutic benefit over immunosuppression in milder disease. The predominance of pauci-immnue (ANCA-associated) RPGN cases in these trials may account for these beneficial results and therefore it is unclear what effect TPE has on immune complex RPGN.

Evidence of efficacy of TPE in most causes of immune-complex RPGN is lacking. There are some reports of TPE efficacy in RPGN due to IgA nephropathy; these include short-term improvement in renal function and delay in dialysis dependency. Randomized trials of TPE in lupus nephritis have shown no benefit. TPE in cryoglobulinemia has proven successful in several series (See fact sheet on cryoglobulinemia).

A single trial of 44 RPGN patients (6 with anti-GBM, 33 with pauci-immune RPGN and 5 with immune-complex RPGN), compared TPE to immunoadsorption using a Staphylococcal protein A agarose column. No difference was found in outcomes between the two treatment groups with both demonstrating improvement.

Technical notes

As stated above, TPE may be beneficial in dialysis-dependent patients at presentation.

Volume treated: 1 to 1.5 TPV	**Frequency:** every other day
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

Treatment for 1–2 weeks followed by tapering with less frequent treatments. The duration of therapy is not well defined in the literature. Some trials have stopped TPE if there is no response after 4 weeks of therapy as outlined above.

References [94,97–99,367,368]

*As of October 8, 2009 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and rapidly progressive glomerulonephritis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

INFLAMMATORY BOWEL DISEASE

Incidence: 2–20 per 100,000/year				Procedure	Recommendation	Category
				Adsorptive cytapheresis	Grade 2B	II

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
9 (721)	4 (183)	12 (881)	NR	Type I

Description of the disease

Ulcerative colitis (UC) and Crohn's Disease (CD) are chronic inflammatory diseases of the gastrointestinal tract and are collectively known as Inflammatory Bowel Disease (IBD). The incidence of IBD is highest in North America and Europe (particularly Scandinavia), however, it has a world wide distribution. Dysfunction of the immune system, in addition to genetic, environmental, and physiologic factors contributes to the pathogenesis of IBD. Histological abundance of leukocytes and monocytes in the mucosa of the bowel incriminate these cells, along with accompanying cytokines and proinflammatory mediators, in the disease process. The phenotype of these disorders is variable affecting predominately individuals in the third decade of life. Because of the progressive and debilitating natural history of IBD, long-term therapy to induce and maintain clinical remission is desirable. A disease activity index (DAI) has been used to standardize and quantify clinical parameters present during active illness in order to monitor response to treatment.

Current management/treatment

In order to target inflammatory process, aminosalicylates are typically the first-line therapy. For moderate to severe IBD, corticosteroids are frequently required to control the disease. Unfortunately, complications from chronic administration include steroid resistance, dependency and the sequelae of long-term steroid use. For those patients who become steroid resistant, immunosuppressive drugs such as azathioprine and 6-mercaptopurine are used. In CD, infliximab, monoclonal antibody to anti-tumor necrosis factor, may induce remission and has been FDA cleared for this purpose. Surgical intervention may be necessary in some patients. Selective apheresis is emerging as a potentially useful adjunct for the management of IBD.

Rationale for therapeutic apheresis

Because of evidence suggesting that granulocytes and monocytes (GM) are pathogenic and the degree of GM infiltration correlates with severity of disease, therapies targeting GM and accompanying inflammatory mediators have been studied. Randomized controlled clinical trials of selective apheresis have demonstrated clinical improvement in IBD patients, including those who are steroid resistant. Reported benefits have included a higher percentage of patients improving compared to placebo controls, more rapid remission of disease than controls, greater measurable improvement in disease activity index (DAI) and fewer adverse reactions than with steroid treatment alone. Endoscopic evidence of healing and diminished leukocyte infiltrates in bowel mucosa by histology has also been reported. Selective apheresis may also be useful as a steroid sparing adjunct. Immunomodulatory effects including reduction in levels of a variety of cytokines (TNF-α, IL-6, IL-8, and IL-1β) may suggest selective apheresis may mitigate IBD pathogenesis. Adverse reactions have been infrequently reported and include headache, fatigue, nausea, arm pain, hematoma, and light-headedness. Results of a placebo-controlled trial performed in North America did not demonstrate efficacy for induction of clinical remission or response in patients with moderate-to-severe UC. In a subsequent randomized non-blinded controlled study in asymptomatic patients, selective apheresis relapses occurred more frequently and earlier in the control group than the treatment group.

Technical notes

Two types of selective apheresis devices are the Cellsorba^{TM} (Asahi Medical, Tokyo, Japan) which is a column containing cylindrical non-woven polyester fibers and, the Adacolumn$^{®}$ (JIMRO, Japan) which contains cellulose acetate beads. Both require anticoagulation (heparin/ACD-A and heparin alone, respectively) to remove granulocytes and monocytes from venous whole blood by filtration/adhesion. For Cellsorba^{TM}, venous whole blood is processed at 50 mL/min through the column for 60 minutes. Some platelets and lymphocytes are also removed by this column. For Adacolumn$^{®}$, venous whole blood is processed at 30 mL/min for 60 minutes. The Adacolumn$^{®}$ is relatively selective for removing activated granulocytes and monocytes. Patients taking ACE inhibitors should not undergo treatment with Adacolumn$^{®}$. Cellsorba^{TM} and Adacolumn$^{®}$ are currently available in Europe and Japan. The two columns have been compared in a prospective clinical trial that demonstrated equivalent response in patients with moderate-to-severe active UC.

Volume treated: 1,800 mL (Adacolumn$^{®}$) or 3,000 mL (Cellsorba^{TM})	**Frequency:** once per week, more intensive therapy may include 2 per week
Replacement fluid: not applicable	

Duration and discontinuation/number of procedures

The typical length of treatment is 5–10 weeks for Adacolumn$^{®}$ and 5 weeks for Cellsorba^{TM}.

References [369–387]

*As of December 31, 2009 using PubMed and the MeSH search terms Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis or IBD and selective apheresis, leukocytapheresis, LCAP, or GMA for articles published in the English language. References of the identified articles were searched for additional cases and trials.

LAMBERT-EATON MYASTHENIC SYNDROME

Incidence: rare				Procedure	Recommendation	Category:
				TPE	Grade 2C	II

# of reported patients*: <100

RCT	CT	CS	CR	Type of evidence
0	0	6 (37)	3 (4)	Type II-3

Description of the disease

The Lambert-Eaton myasthenic syndrome (LEMS) is a myasthenia gravis-like disorder of neuromuscular transmission that is caused by an immune attack on the neuro-muscular junction. The salient features of the disease are muscle weakness, most prominent in proximal muscles of the lower extremities, hyporeflexia, and autonomic dysfunction which may include dry mouth, constipation and male impotence. Muscle weakness, hyporeflexia and autonomic dysfunction constitute a characteristic triad of the syndrome. In contrast to myasthenia gravis, brain stem symptoms such as diplopia and dysarthria are uncommon. LEMS typically presents in mid to late life (age 40 to 79 years) and should be suspected in patients, particularly smokers, with typical symptoms and in patients with unexplained ventilatory failure or prolonged apnea after anesthesia. Approximately 60% of patients have small cell lung cancer that may not become radiographically apparent for 2–5 years after the onset of the neurological syndrome. Lymphoma, malignant thymoma, and carcinoma of breast, stomach, colon, prostate, bladder, kidney, and gallbladder have been reported in association with the syndrome. LEMS is estimated to occur in 3 to 6% of patients with small cell lung cancer, but as many as 44% may have neuromuscular or autonomic deficits that are not sufficient to make the diagnosis of LEMS. Rapid onset and progression of symptoms over weeks or months should heighten suspicion of underlying malignancy. A diagnostic hallmark of LEMS is the presence of autoantibodies directed at the voltage-gated calcium channel (VGCC) of the nerve terminal in upward of 75% of cases of LEMS with primary lung cancer, in up to 25% of LEMS with other forms of cancer, in up to 50% of LEMS patients without cancer, and in up to 10% of lung cancer patients without LEMS. Antibody levels do not correlate with severity but may fall as the disease improves in response to immunosuppressive therapy. These antibodies are believed to cause insufficient release of acetylcholine quanta by action potentials arriving at motor nerve terminals. Unlike myasthenia gravis, which is characterized by antibodies to the postsynaptic acetylcholine receptor, VGCC antibodies target a pre-synaptic structure.

Current management/treatment

Apart from a search for, and treatment of, underlying malignancy, management of LEMS is directed toward support immunosuppression to control production of the offending antibodies and support of acetylcholine-mediated neurotransmission to improve neurological function. Cholinesterase inhibitors such as pyridostigmine (Mestinon) tend to be less effective given alone than they are in myasthenia gravis but can be combined with agents, such as guanidine hydrochloride, that act to enhance release of acetylcholine from the presynaptic nerve terminal. Guanidine hydrochloride is taken orally in divided doses up to 1,000 mg/day in combination with pyridostigmine. Higher doses risk serious side effects including bone marrow suppression, renal tubular acidosis, interstitial nephritis, pancreatic dysfunction, cardiac arrhythmias, and neuropsychiatric changes. 4-aminopyridine, which prolongs stimulation of the voltage-gated calcium channel thus producing an increase in neurotransmitter (acetylcholine) release, may cause seizures in clinically useful doses and therefore is not widely used. 3,4-diaminopyridine, is less prone to cause seizures, is effective therapy in LEMS and may be combined with pyridostigmine. Its efficacy has been demonstrated in a prospective, double-blind, placebo-controlled crossover study of 12 patients, 7 of whom had cancer. Another randomized, double-blind placebo-controlled, crossover study of 9 patients with LEMS demonstrated the efficacy of 3,4-diaminopyridine, but not of pyridostigmine, and further demonstrated no synergistic effect when the two drugs were used in combination. Several clinical trials of 3,4-diaminopyridine in the treatment of LEMS are currently under way in the United States. When approved for use by the FDA, 3,4-diaminopyridine may become first line therapy for many patients. Immunosuppression with prednisone or prednisolone starting at 1 to 1.5 mg/kg on alternate days, or azathioprine starting at 50 mg/day and increased over several weeks to 2–2.5 mg/kg/day in divided doses (with careful monitoring for hematological and other toxicities), is also useful. The immunosuppressants cyclosporine and cyclophosphamide have also been used. Intravenous IgG (IVIG) has been shown effective in LEMS in a randomized, double-blind, placebo-controlled crossover trial involving 9 patients. IVIG may be useful in repeated monthly infusion of 2 g/kg given over 2–5 days over upward of 2 years.

Rationale for therapeutic apheresis

The identification of LEMS as an autoantibody-mediated syndrome has led to several attempts to use therapeutic plasma exchange in its treatment. Reports of benefit were tempered by the observation that the benefit accrued more slowly than was typical in patients with classical myasthenia gravis. In addition, patients tended to worsen after completion of TPE if additional immunosuppressive therapy was not employed. Plasma exchange may be a useful adjunct to management of patients with LEMS whose neurological deficit is severe or rapidly developing, or in the case of patients who are too uncomfortable to wait for immunosuppressive or aminopyridine drugs to take effect, or who cannot tolerate treatment with IVIG.

Technical notes

The reported TPE regimens vary from 5-15 daily TPE over 5-19 days to 8-10 TPE carried out at 5-7 day intervals. Most reports indicate an exchange volume of 1.25 plasma volumes. Of note: improvement may not be seen for the 2 weeks or more after initiation of plasma exchange therapy. This may be due to the slower turnover of the presynaptic voltage gated calcium channel compared to the postsynaptic acetylcholine receptor.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily to every other day
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

Treatment should continue until a clear clinical and EMG response is obtained or at least until a 2–3-week course of TPE has been completed. Repeated courses may be applied in case of neurological relapse, but the effect can be expected to last only 2 to 4 weeks in the absence of immunosuppressive drug therapy.

References [56,388–399]

*As of September 5, 2009, using PubMed and MeSH search terms Lambert-Eaton Myasthenic Syndrome and apheresis for journals published in the English language. References of the identified articles were searched for additional cases and trials.

LUNG ALLOGRAFT REJECTION

Incidence: Chronic rejection: 28% at 2 years, 50% at 5 years, and 74% at 10 years	**Procedure** ECP	**Recommendation** Grade 1C	**Category** II

# of reported patients*: 100–300

RCT	CT	CS	CR	Type of evidence
0	0	8 (167)	5 (5)	Type II-3

Description of the disease

Based on recent International Society of Heart and Lung Transplantation (ISHLT) registry data, 2,700 procedures were performed in 2007. Between 7/2004 – 6/2008, 36% of recipients were treated for acute rejection which typically occurs in the first 6-12 months after transplantation. Improved diagnosis and treatment has decreased the risk of death from acute rejection from 4.3% at 30 days to 1.8% at 1 year. Acute rejection is one of the major risk factors for chronic rejection which remains the most common cause of death after the first year of transplant. Chronic rejection is manifested as bronchiolitis obliterans syndrome (BOS). BOS is a pathological process that affects small airways and is a significant cause of allograft chronic dysfunction. BOS can be difficult to diagnose by transbronchial biopsy and thus the diagnosis is made on the basis of graft deterioration due to persistent airflow obstruction instead of histologic confirmation. BOS is characterized clinically by progressive dyspnea and airflow limitation with declining forced expiratory volume in 1 second (FEV_1) that cannot be explained by other causes such as acute rejection or infection. According to the ISHLT staging system for BOS, Stage 0 refers to no significant abnormality and $FEV_1 \geq 90\%$ of best postoperative value, while Stage 3 refers to severe BOS with $FEV_1 \leq 50\%$. Potential BOS (0-p) defined as FEV_1 81-90%, was added to detect early changes in graft function that might predict the onset of stage 1. BOS is a major factor limiting long-term survival after lung transplantation, which is approximately 50% at 5 years.

The most precipitous decline in airflow typically occurs in the first six months following a diagnosis of BOS, although time of onset of BOS and rate of decline of FEV_1 are highly variable. Single lung transplantation conveys a higher risk for earlier onset of BOS compared with bilateral transplantation, and an unfavorable outcome appears to be associated with rapid onset of BOS, female gender, and pretransplant idiopathic pulmonary fibrosis.

Current management/treatment

At the time of transplantation, many transplant centers now employ an induction regimen that includes infusion of an antibody that targets activated host lymphocytes. Such agents include polyclonal anti-T-cell preparations like antithymocyte globulin (ATG), or monoclonal agents aimed at lymphocyte surface molecules such as CD3 (OKT3), IL-2 receptor/CD25 (daclizumab, basiliximab) or CD52 (Campath-1H). Maintenance immunosuppressive therapy after lung transplantation typically consists of a three-drug regimen that includes a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate mofetil), and steroids. Short courses of intravenously pulsed corticosteroids, followed by a temporary increase in maintenance doses for a few weeks, are the preferred treatment for uncomplicated acute rejection. The initial treatment of BOS usually consists of repeated pulses of high-dose methylprednisolone. Additional therapeutic options are augmentation of existing regimens and/or switching within classes of drugs. Successful treatment of BOS is usually defined as ''stabilization'' or ''slowing'' of FEV_1 decline instead of true improvement or normalization of airflow. For patients with unresponsive BOS, salvage immunosuppressive regimens have included methotrexate, ATG, or OKT3. Recently, the macrolide antibiotic azithromycin has shown efficacy in improving FEV_1 in lung transplant recipients suffering from BOS.

Rationale for therapeutic apheresis

The first report of extracorporeal photochemotherapy (ECP, also referred to as photopheresis) in a lung transplant patient was published in 1995. At first, ECP was used in the context of refractory BOS (Stages 2-3) in which beneficial effect was demonstrated by initial stabilization or improvement in FEV_1. Since then, the literature suggested that ECP may be an effective therapeutic modality for stabilization of lung function in patients with persistent acute rejection and early BOS (Stages 0-p -1), thus preventing further loss of pulmonary function. As ECP is not likely to reverse fibroblast proliferation in the transplanted lung, earlier initiation of ECP may arrest BOS progression thereby inducing improvement in the patient's clinical status and FEV_1. Two recent largest studies to date (60 and 24 patients) showed that ECP significantly reduced the rate of decline in lung function in transplant recipients with BOS in all stages as measured by FEV_1.

Although the mechanism of action remains unclear, possible explanations for the beneficial effects of ECP in transplantation include: stimulation of production of clone–specific suppressor T cells; induction of lymphocyte apoptosis and alterations in the T-cell receptor; release of inflammatory mediators (IL-1, IL-6 and TNF-α) by ECP-treated monocytes, affecting the entire immune system population, and induction of immunomodulation via regulatory T cells (Tregs) which suppress immune reactions in an antigen-specific fashion. A recent study showed that ECP slightly increased or stabilize the number of peripheral CD4+CD25+Fox3+ Treg cell counts in lung transplant recipients who showed functional stabilization.

Overall, the reinfusion of the treated leukocytes mediates a specific suppression of both the humoral and cellular rejection response, and thereby induces tolerance of the allograft, thus prolonging the survival of transplanted tissues and organs. Importantly, ECP is well tolerated and is not associated with an increased risk of infection, a common complication of immunosuppressant drugs.

Technical notes

One treatment cycle consists of ECP on two consecutive days. A common regimen includes one cycle every two weeks for the first two months, followed by once monthly for two months (total of 6). In recent large series: total of 24: 10 during first month, biweekly for 2 months and then monthly for 3 months.

Volume treated: An MNC product of 200 - 270 mL. The two step process method collects and treats MNCs obtained from 2-times TBV processing.	**Frequency:** Variable. Biweekly to every two weeks. Larger intervals of every 4 to 6 weeks have been also reported.
Replacement fluid: N/A	

Duration and discontinuation/number of procedures

The optimal duration remains unanswered. The number of treatment cycles ranged between 6-24. If clinical stabilization occurs with ECP, long-term continuation might be warranted to maintain the clinical response. In a recent 10 year single center experience, 12 cycles were the initial ''dose'' and long term continuation was recommended for responders.

References [173,174,400–412]

*As of September 26, 2009 using PubMed and the MeSH search terms lung transplantation and extracorporeal photochemotherapy or photopheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

MALARIA

Incidence: Estimated 247 million cases in 2006. 1500 cases (1 death) of imported malaria in the U.S. in 2007	Procedure RBC exchange	Recommendation Grade 2B	Category II (severe)

# of reported patients*: <100 RBC exchange; >300 Manual exchange transfusion

	RCT	CT	CS	CR	Type of evidence
RBC Exchange	0	0	7 (29)	7 (9)	Type II-3
Manual exchange transfusion	0	8 (279)	7 (76)	13 (13)	Type II-2

Description of the disease

Malaria is a vector-borne protozoal infection caused by *Plasmodium vivax, P. ovale, P. malariae* or *P. falciparum*. Malaria accounted for an estimated 881,000 deaths in 2006 with 91% occurring in Africa, where *P. falciparum* is highly prevalent, and 85% were children under 5 years of age. The *Plasmodia* life cycle includes an intraerythrocytic stage of reproduction, which is responsible for many of the pathological manifestations of the disease and the vehicle for transmission by mosquitoes or blood transfusion. The standard diagnostic test for malaria involves identification of typical intraerythrocytic organisms on thick or thin blood smears. An FDA approved rapid diagnostic immunoassay is also available. Infectious symptoms usually begin within 10 days to 4 weeks after inoculation by an infected mosquito. Parasitemia leads to hemolysis and activation of inflammatory cells and cytokines that cause fever, malaise, chills, headache, myalgia, nausea, vomiting and, in some cases, anemia, jaundice, hepatosplenomegaly and thrombocytopenia. *P. falciparum* is responsible for most of the severe and fatal malaria cases, usually in the setting of high-grade parasitemia, disseminated microcirculatory occlusion and multisystem dysfunction. Severe malaria, which incurs an overall mortality rate of 15-20% in treated patients, is characterized by impaired consciousness/coma, multiple seizures, pulmonary edema, acute respiratory distress syndrome, shock, disseminated intravascular coagulation, spontaneous bleeding, renal failure, jaundice, hemoglobinuria, severe anemia (Hgb <5 g/dL) acidosis, other metabolic derangements and/or parasitemia >5%. Nonimmune hosts (i.e. travelers with inadequate chemoprophylaxis), children and pregnant women with parasitemia >10% are at greatest risk. *P. falciparum* is now the most common etiology of ''imported'' malaria in nonendemic countries. Because severe complications can develop in up to 10% of cases, symptomatic patients with a positive travel history should be promptly evaluated and treated.

Current management/treatment

Malaria treatment is based on the clinical status of the patient, the *Plasmodium* species involved and the drug-resistance pattern predicted by the geographic region of acquisition. Management of imported, uncomplicated malaria in the U.S. is outlined in guideline documents available from the Centers for Disease Control (CDC). Single or combination oral agent regimens include chloroquine, hydroxychloroquine or quinine (alone or with doxycycline, tetracycline or clindamycin), atovaquone-proguanil, artemether-lumefantrine, mefloquine and primaquine. Artesunate is available through the CDC for drug-resistant strains. Severe malaria should be treated promptly with intravenous quinidine gluconate or quinine plus doxycycline, tetracycline or clindamycin. Falciparum malaria with more severe anemia, hypoxemia, hyperparasitemia, neurologic manifestations (i.e. cerebral malaria) or metabolic derangements, particularly in children, asplenic or immunocompromised individuals, requires aggressive parenteral antimalarials and supportive care in an intensive care unit to manage volume resuscitation, electrolyte replacement, antiseizure medications, transfusion as indicated, airway control and/or ventilatory maintenance.

Rationale for therapeutic apheresis

RBC exchange or manual exchange transfusion (with whole blood or red cell replacement) in severely ill patients with hyperparasitemia (i.e. >10%) are believed to improve blood rheological properties (especially with cerebral malaria) and to reduce pathogenic mediators such as parasite-derived toxins, hemolytic metabolites and cytokines. A number of reports and small case series have described rapid clinical improvement of severe *P. falciparum* malaria after RBC exchange or manual exchange transfusion, when used in conjunction with antimalarial therapy. However, a meta-analysis of 279 patients from 8 case-controlled trials found no survival benefit of manual exchange transfusion compared to antimalarials and aggressive supportive care alone. Notably, the exchange transfusion methods in those trials were not comparable, the patients in the transfusion groups were more ill, additional differences in treatment populations and confounding variables were not adjusted in the analysis and other important outcomes, such as duration of coma and severe end-organ complications (i.e. severe malaria), were not assessed. Despite these observations and the lack of randomized controlled trials, the CDC recommends consideration of adjunctive RBC exchange if parasitemia is >10% or if the patient has severe malaria manifested by non-volume overload pulmonary edema, renal complications or cerebral malaria. Quinidine administration should not be delayed for the procedure and can be given concurrently. The U.K. treatment guidelines of severe malaria also suggest consideration of RBC exchange for severely ill patients with >10% parasitemia. The WHO guidelines make no recommendation regarding the use of exchange transfusion, citing the lack of comparative trials and consensus on indications, benefits and dangers. Rare case reports have described the use of adjunctive plasma exchange with automated red cell exchange; however, lack of published experience precludes assessment of this procedure in patients with severe malaria.

Technical notes

Automated apheresis instruments calculate the amount of RBCs required to achieve the desired post-procedure hematocrit, fraction of red cells remaining and, by inference, the estimated final parasite load. A single two-volume RBC exchange can reduce the fraction of remaining patient red cells to roughly 10-15% of the original. The risks include circulatory overload, transfusion reactions, blood-borne infection (especially in developing countries), hypocalcemia, red blood cell allosensitization and possible need for central venous access.

Volume treated: 1 to 2 total red blood cell volumes	**Frequency:** usually one to two treatments
Replacement fluid: leukoreduced RBCs, plasma	

Duration and discontinuation/number of procedure

Treatment is discontinued after achieving <5% residual parasitemia. Treatment should be continued for higher parasite levels with ongoing signs and symptoms of severe infection.

References RBC Exchange [146,334,413–439]

Manual exchange transfusion [146,414,416,430–441]

*As of October 15, 2009 using PubMed and the MeSH search terms malaria, falciparum, apheresis, erythrocytapheresis, red cell exchange, and hyperparasitemia for reports published in the English language. References of the identified articles were searched for additional cases and trials.

MULTIPLE SCLEROSIS

Incidence: 5-30 per 100,000/year in the US	Procedure	Recommendation	Category
	TPE	Grade 1B	II (Acute CNS inflammatory demyelinating disease unresponsive to steroids)
	TPE	Grade 2B	III (Chronic progressive MS)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
Acute CNS inflammatory demyelinating disease	3 (306)	1 (41)	5 (56)	5 (5)	Type I
Chronic progressive MS	7 (285)	0	10 (165)	3 (4)	Type I

Description of the disease

Multiple sclerosis (MS) is a relapsing and often progressive disorder of central nervous system (CNS) white matter demyelination. It presents in early adulthood and has variable prognosis. Eighty percent of MS is the relapsing-remitting form where signs and symptoms evolve over days, stabilize and then improve within weeks. Corticosteroids speed recovery, but the response decreases over time. Persistent symptoms may develop and the disease may progress between relapses, referred to as secondary progressive MS. Alternatively, 20% of MS patients have a primary progressive form with continuous progression without improvement. Clinical symptoms include sensory disturbances, unilateral optic neuritis, diplopia, limb weakness, gait ataxia, neurogenic bladder and bowel symptoms. MRI shows multiple lesions of different ages involving the white matter of the cerebrum, brain stem, cerebellum, and spinal cord. A more severe clinical course can be predicted by frequent relapses in the first 2 years, primary progressive form, male sex, and early permanent symptoms. Acute central nervous system inflammatory demyelinating disease is usually secondary to MS but includes cases of acute transverse myelitis and neuromyelitis optica (NMO or Devic'syndrome). NMO is discussed in a separate fact sheet.

Current management/treatment

Genetic and environmental factors play a role in the pathogenesis of MS. It is believed to be an autoimmune disorder, with involvement of both the humoral and cellular components of the immune system. In acute, severe attacks of MS in patients who fail initial treatment with high-dose steroids, TPE may be beneficial.

Treatment in relapsing-remitting MS includes: azathioprine, intravenous immunoglobulin, interferon β-1a, glatiramer acetate, mitoxantrone hydrochloride, natalizumab, and cyclophosphamide depending on the disease severity. TPE has not been specifically studied in relapsing-remitting MS.

An adequate treatment for primary progressive MS does not exist. Multiple randomized controlled trials demonstrate small to no benefit of TPE in conjunction with other immunosuppressive drugs in patients with chronic progressive MS. It is not clear whether the cost and potential adverse effects of TPE outweigh the potential small benefit.

Rationale for therapeutic apheresis

MS is an autoimmune disease with an unclear pathogenesis. TPE may benefit MS patients by removing an autoantibody, such as anti-myelin antibody, or modulating immune response. There have been four immunopathological patterns of demyelination in early MS lesions. The characteristics of demyelination for each pattern are: type I - T-cell/ macrophage-associated, type II - antibody/ complement-associated, type III - distal oligodendrogliopathy, and type IV - oligodendrocyte degeneration. A study of patients with fulminant CNS inflammatory demyelinating disease demonstrated that all 10 patients with type II but none of the 3 with type I or 6 with type III had substantial improvement with TPE.

Technical notes

See the introduction to this article.

Volume treated: 1 to 1.5 TPV **Replacement fluid:** albumin	**Frequency:** acute 5 to 7 over 14 days, chronic progressive weekly

Duration and discontinuation/number of procedures

In acute MS unresponsive to steroids, 5 to 7 TPE procedures have a response rate of approximately 50%. In chronic progressive MS, TPE could be a long-term therapy, if shown to be of benefit, with tapering as tolerated.

References [442–448]

*As of November 11, 2009 using PubMed and the MeSH search terms multiple sclerosis and plasma exchange or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

MYASTHENIA GRAVIS

Incidence: 1 per 100,000/year		Procedure	Recommendation	Category
		TPE	Grade 1A	I (moderate and severe)
		TPE	Grade 1C	I (pre-thymectomy)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
moderate and severe	7 (181)	4 (114)	30 (556)**	NA	Type I
pre-thymectomy	0	5 (342)	2 (51)**	NA	Type II-2

**6(405) case series contained both groups of patients.

Description of the disease

Myasthenia gravis (MG) is an autoimmune disease characterized by weakness and fatigability with repetitive physical activity, which usually improves with rest. Common presentation includes ptosis and diplopia with more severe cases having facial, bulbar, and limb muscle involvement. The disease is more prevalent in 20-40 year old women. The causative antibody is usually directed against the acetylcholine receptor (anti-AChR) on the post-synaptic surface of the motor end plate. Ordinarily, motor nerves release the neurotransmitter acetylcholine at the neuromuscular junction. The neurotransmitter crosses the synaptic space to the muscle surface where it binds the acetylcholine receptor and stimulates an action potential and muscle contraction. Anti-AChR reduces the number of available acetylcholine receptors, thus decreasing the action potential achieved with stimulation. 80-90% of MG patients have detectable anti-AChR. Other factors might play a role in the disease as antibody level does not correlate with disease severity and severe disease can occur without detection of this antibody. Antibodies to the muscle specific receptor tyrosine kinase (MusK) are present in about 50% of patients without anti-AChR. MuSK mediates formation of the neuromuscular junction and induction of the AChR. The remainder of seronegative individuals may have these antibodies at levels undetectable using current laboratory methods, or they may have other autoantibodies that act at the neuromuscular junction. Myasthenic crisis is characterized by acute respiratory failure requiring intubation, prolonged intubation following thymectomy, or bulbar weakness causing dysphasia and high risk of aspiration. Thymic abnormalities, such as hyperplasia or thymoma, are commonly associated with MG.

Current management/treatment

With modern treatment regimens the mortality from MG has greatly decreased from 30% to less than 5%. The four major treatment approaches include cholinesterase inhibitors, thymectomy, immunosuppression, and either plasma exchange (TPE) or intravenous immunoglobulin. Cholinesterase inhibitors (e.g. pyridostigmine bromide) delay the breakdown, and increase the availability, of acetylcholine at the motor end plate and lead to variable improvement in strength. Cholinergic side affects, including diarrhea, abdominal cramping, increased salivation, sweating and bradycardia, can be dose limiting and lead to non-compliance. Thymectomy leads to clinical improvement in many patients under the age of 65 but it may take years for the benefits to show. Immunosuppressive drugs (corticosteroids, azathioprine, cyclosporine, and tacrolimus) have a delayed effect and therefore play an important role in long-term rather than short-term management.

Rationale for therapeutic apheresis

TPE is used principally to remove circulating autoantibodies, although both seropositive and seronegative patients respond to TPE. TPE is especially used in myasthenic crisis, perioperatively for thymectomy, or as an adjunct to other therapies to maintain optimal clinical status. TPE works rapidly; clinical effect can be apparent within 24 hours but may take a week. The benefits will likely subside after 2 to 4 weeks, if immunosuppressive therapies are not initiated to keep antibody levels low.

Two randomized controlled trials (RCT) compared IVIG and TPE. One trial randomized 87 patients with major exacerbations to 3 every-other-day 1.5 volume TPE, 0.4g/kg/day × 3 days of IVIG, or 0.4g/kg/day × 5 days of IVIG. All 3 arms were equivalent at day 15. A second RCT that included 12 stable patients with moderate to severe disease found TPE to be better at 1 week, equivalent improvement at 4 weeks, and neither to show improvement at 16 weeks. A retrospective multicenter chart review of 54 myasthenic episodes compared the two treatment modalities for myasthenic crisis. Patients received either 5 or 6 plasma exchanges of 25-45 ml/kg on alternate days or 0.4g/kg/day × 5 days of IVIG. TPE resulted in significantly more improvement than IVIG in ventilatory status at 2 weeks and overall outcome at 1 month. In the two larger studies adverse effects of TPE were more frequent (hypotension, bleeding/hematoma, thrombosis, nausea/vomiting) in comparison to IVIG (headache, renal failure, nausea/vomiting). In a RCT of daily versus every-other-day double filtration plasmapheresis (1 TPV) the daily regimen was more effective in reducing an overall disability score. Another RCT showed daily to be equivalent to every-other-day small volume exchanges (20-25 ml/kg). Clinical trials have reported on the use of TPE prior to thymectomy: most studies have shown improved patient outcome with routine use of TPE but other studies have shown equivalent outcomes with selective TPE use in patients at high-risk for prolonged intubation post-thymectomy.

Technical notes

See the introduction to this article

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

A typical induction regimen consists of processing 225 ml/kg of plasma over a period of up to two weeks but smaller volumes process can be beneficial. The number and frequency of procedures depend upon the clinical scenario. Some patients may require long-term maintenance TPE.

References [449–455]

*As of November 2, 2009 using PubMed and the MeSH search terms myasthenia gravis and plasmapheresis and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

MYELOMA CAST NEPHROPATHY

Incidence: 1 per 100,000/year				**Procedure**	**Recommendation**	**Category**
				TPE	Grade 2B	II** (cast nephropathy)

# of reported patients*: 100-300

RCT	**CT**	**CS**	**CR**	**Type of evidence**
5 (182)	0	6 (105)	7(10)	Type I

Description of the disease

Renal failure develops in up to 50% of patients with multiple myeloma and shortens their survival. Myeloma kidney (cast nephropathy) accounts for approximately 30-80% of such cases, depending on the class of M-protein. Autopsy studies show distal renal tubules obstructed by laminated casts composed of light chains (Bence-Jones protein), albumin, Tamm-Horsfall protein and others. As tubular obstruction progresses the decline in renal function becomes irreversible. Hypotheses regarding the mechanism of pathological distal tubule cast formation focus on an increase in light chain concentration in the distal tubular urine. This may result from the overwhelming of proximal tubule processing of light chains when light chain production is rising due to tumor progression Other contributing factors may include hypercalcemia, hyperuricemia, dehydration, intravenous contrast media, toxic effects of light chains on distal tubular epithelium, etc.

Current management/treatment

Therapeutic approaches rely on inducing an alkaline diuresis through intravenous administration of normal saline and sodium bicarbonate with or without loop diuretics (e.g. furosemide or equivalent) in order to solublize positively charged light chains. Anti-myeloma chemotherapy consisting of an alkylating agent with a corticosteroid is used to diminish M-protein production. More recently, immune modulation (thalidomide, lenalidomide) and proteosome inhibition (bortezomib) have emerged as effective therapy. Supportive care with hemodialysis or peritoneal dialysis is employed as needed.

Rationale for therapeutic apheresis

Although chemotherapy and alkaline intravenous fluid are the primary modes of therapy, plasma exchange has been used to acutely decrease the delivery of light chains to the renal glomerulus for filtration. Peritoneal dialysis (but not hemodialysis) can also remove light chains but with lower efficiency than plasma exchange. A randomized trial of 21 patients with biopsy-proven myeloma kidney (cast nephropathy) who received melphalan, prednisone and forced diuresis with or without plasma exchange showed no statistically significant outcome differences. However, among a dialysis-dependent subgroup, 43% in the plasma exchange group and none in the control group recovered renal function. In particular, biopsy findings that indicated potential reversibility (e.g. absence of fibrosis of all affected glomeruli) were important predictors of success. This led to an endorsement of plasma exchange for myeloma kidney by the Scientific Advisors of the International Myeloma Foundation. The largest randomized trial of chemotherapy and supportive care with or without plasma exchange failed to demonstrate that 5 to 7 plasma exchange procedures over 10 days substantially reduces a composite outcome of death, dialysis dependence or estimated glomerular filtration rate of <30 ml/min/1.73 m^2 at 6 months. This study has called into question the role of plasma exchange in the treatment of myeloma kidney in an era of rapidly effective chemotherapy. On the other hand, this study has been criticized in that most of the enrolled patients were not proven to have cast nephropathy by renal biopsy, confidence intervals were wide, suggesting the study was underpowered, and the composite outcome undervalued an end result of dialysis independence for many patients. Survival at six months, as opposed to end points more specific to recovery of renal function, has also been questioned as part of the composite outcome. More recent data suggest that plasma exchange has only transient effects on serum free light chains as measured using a clinically available assay. Biopsy-proven cast nephropathy may be an important supportive finding if plasma exchange is contemplated.

Technical notes

Initial management, especially in the case of nonoliguric patients, should focus on fluid resuscitation (2.5-4 liters/day), alkalinization of the urine and chemotherapy. If serum creatinine remains elevated after several days, consider addition of plasma exchange. For patients who are oliguric, who excrete ≥10 grams of light chains per 24 hours, or whose serum creatinine is ≥6 mg/dL, plasma exchange may be included in initial management, especially in the case of light-chain myeloma. All of the published studies combine plasma exchange with chemotherapy and other forms of supportive care described above. Published studies vary with respect to treatment schedules and replacement fluids employed for plasma exchange. If plasma exchange and hemodialysis are to be performed on the same day, they can be performed in tandem (simultaneously) without compromising the efficiency of the hemodialysis procedure.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin; albumin/saline	

Duration and discontinuation/number of procedures

Controlled trials have employed plasma exchange as a short-term adjunct to chemotherapy and fluid resuscitation over a period of 2-4 weeks. In some studies and reports, a course of plasma exchange, (10-12 procedures over 2-3 weeks), may be repeated depending on the patient's clinical course.

References [126,456–473]

*As of August 31, 2009, using PubMed and MeSH search terms multiple myeloma, renal disease and apheresis for journals published in the English language. References of the identified articles were searched for additional cases and trials.
** **Comments:** There are no studies that compare one apheresis treatment schedule with another, but the randomized trials referenced above rely on short periods of daily treatment. Smaller trials have demonstrated improved 1-year survival in the groups whose treatment included plasma exchange, the largest, randomized trial did not demonstrate improved survival at six months. In all cases ultimate survival depends on a satisfactory response to chemotherapy.

NEPHROGENIC SYSTEMIC FIBROSIS

Incidence: rare				Procedure	Recommendation	Category
				ECP	Grade 2C	III
				TPE	Grade 2C	III

# of reported patients*: <100

	RCT	CT	CS	CR	Type of evidence
ECP	0	0	5 (17)	1	Type II-3
TPE	0	0	5 (11)	1	Type II-3

Description of the disease

Nephrogenic systemic fibrosis (NSF) is a systemic disorder seen in patients with acute or chronic renal failure within 2 months of the administration of gadolinium (Gd) containing contrast agents. It has also been seen in patients with hepatorenal syndrome and in the perioperative period following liver transplantation. It occurs in 2 to 7% of patients with chronic renal failure receiving Gd contrast agents. 95% of cases have been in patients with stage 4 (GFR=10-29 ml/min/1.73m^2) or stage 5 (dialysis dependent) chronic renal failure. It has not been seen in those with a GFR >60 ml/min/1.73m^2. Additional factors associated with NSF include thromboembolism, surgery, systemic infections, hypercoaguable states, metabolic acidosis, high erythropoietin levels, and elevations in calcium, iron, zinc, copper, and phosphate.

NSF involves the skin and consists of a symmetrical erythematous rash, non-pitting edema, paresthesias, and pruritis involving the extremities. Additional findings may include hair loss, gastroenteritis, conjunctivitis, bilateral pulmonary infiltrates, and fever. Over 6 to 12 months, the swelling, pruritus, and sensory changes resolve while the skin progresses to a thickened, hardened dermis/subcutis with epidermal atrophy. Fibrosis results in joint contractures leading to wheel chair dependence and may extend into deeper tissues including skeletal muscle, heart, pericardium, pleura, lungs, diaphragm, esophagus, kidneys, and testes. In 5% of patients, the disease progresses rapidly to death within weeks to months while the remaining demonstrate slow progression. Overall mortality rate is 30% with death due to restricted mobility and respiratory insufficiency.

The pathophysiology of the disorder is uncertain. Renal failure markedly prolongs Gd contrast excretion. The prolonged elimination results in disassociation of the Gd, which may be further enhanced by metabolic acidosis. Increased phosphate levels and inflammation leads to Gd phosphate tissue deposition. This is taken up by tissue macrophages resulting in pro-inflammatory and pro-fibrotic cytokine production leading to tissue infiltration by circulating fibrocytes and collagen production. Gd may also directly stimulate fibroblasts.

Current management/treatment

Replacement of renal function through renal transplant has been associated with cessation of progression and reversal. It should be noted that dialysis has not been associated with improvement. Additional therapies which have been used include steroids, imatinib messylate, chelation therapy with sodium thiosulfate, plasma exchange, and extracorporeal photopheresis.

Rationale for therapeutic apheresis

Due to the lack of an effective therapy, plasma exchange has been applied. Twelve patients treated with TPE have been described in the literature. Seven patients demonstrated improvement including skin softening (7), increased range of motion (ROM) (4), improved ambulation (1) and improvement from wheel chair bound to walking in one patient. Additional reported changes have included decreased swelling, pain, and paresthesias.

ECP has been applied to NSF because of similarities to symptoms of chronic graft versus host disease and scleromyxedema. Eighteen patients treated with ECP have been described in the literature. Sixteen demonstrated improvement including skin softening (16), increased ROM (12), improved ambulation (4), and improvement from being wheel chair bound to walking in three patients. Additional reported changes have included resolution of skin lesions and decreased pruritis.

Technical notes

Relationship between time of initiation of therapy and reversal of changes is unclear. Whether the changes become irreversible or if earlier treatment is more effective than later has not been determined.

Volume treated:	Frequency:
ECP: An MNC product of 200 - 270 mL. The two step process method collects and treats MNCs obtained from 2-times TBV processing.	ECP: Various schedules ranging from a minimum of 2 consecutive days every 2 to 4 weeks up to 5 procedures every other day (cycle) with increasing number of weeks between cycles (1 to 4) with 4 cycles composing a round.
TPE: 1 to 1.5 TPV	TPE: Various schedules ranging from a minimum of daily for 5 consecutive days up to twice per week for 10 to 14 treatments.

Replacement fluid: ECP: Not applicable; TPE: albumin,

Duration and discontinuation/number of procedures

Time to response has not been reported for most patients treated with TPE. Improvement of early symptoms in one patient reported to have occurred within 3 days of initiation of treatment. Time to response with ECP ranged from 4 to 16 months. Reports have treated patients for a fixed number of procedures as outlined above.

References [474–485]

*As of December 10, 2009 using PubMed and the MeSH search terms nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials. This fact sheet includes abstracts in the summary of published reports and considers them in determining the recommendation grade and category.

NEUROMYELITIS OPTICA

Incidence: rare			Procedure	Recommendation	Category
			TPE	Grade 1C	II

# of reported patients*: <100				
RCT	CT	CS	CR	Type of evidence
0	1 (43)	6 (44)	12 (12)	Type II-3

Description of the disease

Neuromyelitis optica (NMO; Devic's disease) is an inflammatory demyelinating disorder characterized by attacks within the spinal cord and optic nerve. Symptoms of myelitis include paraparesis and sensory loss below the lesion, sphincter loss, dyesthesia, and radicular pain; symptoms of optic neuritis include ocular pain, visual field deficits, and positive phenomena; and symptoms of hypothalamic and brainstem involvement, which occur in 15% of patients, include hiccoughs (hiccups), intractable nausea, and respiratory failure. NMO is more typical in non-whites (African Americans, Asians, and Indians), women, and older age of onset than multiple sclerosis (MS). Distinction from MS is by female predominance (1:4-5 male: female), longitudinal spinal cord lesions (3 or more vertebral segments), and cerebrospinal fluid (CSF) with negative oligoclonal IgG bands and with leukocytosis. In addition brain MRI is not typical for MS. NMO is associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE), Sjögren's, and myasthenia gravis, as well as viral infections and vaccinations. NMO can have either a monophasic or relapsing course. Monophasic course is associated with younger age at disease onset and equal male:female predominance. Monophasic course has a 90% 5 year survival rate. Approximately 80% of patients with NMO have relapsing coarse, which has a poor prognosis: 50% of patients become legally blind or wheelchair bound and 30% die respiratory failure within 5 years. There is not a progressive phase like MS; the disease worsens by incomplete recovery with each acute attack.

Current diagnostic criteria are: optic neuritis, acute myelitis, at least two of three supportive criteria: contiguous spinal cord MRI lesions extending over ≥3 vertebral segments, brain MRI not meeting diagnostic criteria for MS, NMO-seropositive status (sensitivity 94%, specificity 96%).

Current management/treatment

Acute attacks are managed by high-dose intravenous steroids and, if failure to resolve symptoms plasma exchange (TPE) is added. Relapses are commonly resistant to steroids, and TPE can be helpful in recovery from acute attack but does not prevent further relapses. Prophylaxis to prevent further acute attacks includes immunosuppressive medications and immunomodulation, such as rituximab (anti-CD20), methotrexate, interferon, azathioprine, cyclophosphamide, prednisone, intravenous immunoglobulin, mitoxantrone, interferon, and mycophenolate mofetil. Patients at high risk for relapse include those who are seropostive for NMO-IgG.

Rationale for therapeutic apheresis

First, over 70% of cases of NMO are associated with NMO-IgG. NMO-IgG binds to aquaporin-4, a water channel, which is on astrocyte foot processes at the blood brain barrier. Histopathology of NMO includes deposition of IgG and complement in the perivascular space with a granulocyte and eosinophil infiltrate, and hyalinization of vascular walls. The sensitivity of NMO-IgG is dependent on the assay used, but one study determined its sensitivity as 91% and specificity as 100% using an anti-AQP4 antibody assay. Second, TPE has been successfully used in other acute demyelinating disorders, such as acute demyelinating encephalomyelitis. Third, response to TPE in MS is associated with an antibody pattern. TPE removes the pathologic antibody, immune complexes, and inflammatory mediators. Therefore, it is reasonable to postulate TPE has a role in the treatment of NMO. One study determined that men, those who received TPE early after attack (<20 days), and had preserved reflexes were more likely to respond to TPE.

Technical notes

See the introduction to this article.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

The majority of studies performed 5 procedures on average, but ranged from 2 to 20 procedures. In the retrospective cohort study, those who received TPE had lower residual disability scores. In case series 50-70% of patients showed improvement after TPE. All patients had received steroids.

References [40,448,486–491]

*As of November 15, 2009 using PubMed and the MeSH search terms neuromyelitis optica and Devic's and myelitis and optic neuritis and plasma exchange and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

OVERDOSE, VENOMES, AND POISONING

Incidence: rare	Procedure	Recommendation	Category
	TPE	Grade 2C	II (mushroom poisoning)
	TPE	Grade 2C	III (invenomation)
	TPE	Grade 2C	III (MAb/progressive multifocal leukoencephalopathy)
	TPE	Grade 2C	III (other compounds)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
Mushroom poisoning	0	0	10 (296)	4 (4)	Type II-3
Snake bites	0	0	2 (40)	3 (3)	Type II-3
Monoclonal antibodies/Biologics	0	0	1 (12)/1 (28)**	1 (1)	Type II-3
Other compounds	0	0	9 (125)	47 (48)	Type II-3

**potential overlap in reported patients.

Description of the disease

Drug overdose and poisoning, whether accidental, intentional, or iatrogenic, result from excessive exposure to an agent capable of producing tissue injury and/or organ dysfunction. Ingestion, inhalation, and injection are common routes of exposure. The list of agents potentially toxic to humans is enormous and diverse. It is difficult to quantify the morbidity and mortality attributable to these problems. The majority of incidents is accidental and occurs at home, most often involving children under the age of six. Fortunately, serious injury is the exception to the rule. The mechanism of tissue damage varies with the nature of the offending substance and the mode of entrance into the body. Agents may be directly toxic to human tissue or may require enzymatic conversion to an active, injurious metabolite. Local effects at the site of entry into the body may accompany systemic effects, and the onset of symptoms may be rapid or delayed. Initial treatment focuses on supportive care and the removal of the toxic agent.

Current management/treatment

Evaluation and stabilization of the airway, breathing, circulation, and neurologic status are primary concerns. Toxin-specific antidotes, when available, are promptly administered. The physician can choose from a vast array of methods to enhance removal of the toxin, depending on specific characteristics of the agent and the route of exposure. Induced emesis, gastric lavage, and oral administration of activated charcoal may be used to minimize gastrointestinal absorption of ingested substances. Whole-bowel irrigation, another technique available for gastro-intestinal decontamination, is particularly useful for removing poorly absorbed agents that are not adsorbed to charcoal. Forced acid or alkaline diuresis is used to promote the renal elimination of ionized agents that are not strongly bound to proteins. Extracorporeal elimination techniques are also used. Hemodialysis is an effective technique for removing drugs that are not tightly bound to plasma proteins and that readily diffuse through a semi-permeable membrane. Hemoperfusion, a procedure in which blood is passed directly over sorbent particles, can be more effective than dialysis for protein-bound drugs and large molecules. Comprehensive lists of drugs and chemicals removed with dialysis and hemoperfusion have been compiled. Less than 0.04% of poisoned patients were treated with extracorporeal procedures such as hemodialysis, hemoperfusion and others.

Rationale for therapeutic apheresis

TPE is an alternative technique for the removal of protein-bound toxins that are not readily removed with dialysis or hemoperfusion. TPE is effective in removing highly protein-bound toxins from the blood but not from other fluid compartments. Efficiency is limited by the unique characteristics of the toxic substance. Agents that are most amenable to removal by TPE are not lipid soluble or bound to tissue, and do not have a large volume of distribution outside the bloodstream. The clinical benefit can be achieved only if toxin levels can be reduced to concentrations below the threshold for tissue damage. Reports of the successful use of apheresis in the treatment of various drug overdoses and poisonings are generally anecdotal. Interestingly, there is no correlation between protein binding and a volume of distribution among substances which were successfully treated with TPE. This may indicate that other factors played more important role in patients' recovery. There are also case reports of the failure of plasma exchange to remove substances bound to proteins and lipids such as barbiturates, chlordecone, aluminum, tricyclic antidepressants, benzodiazipines, quinine, and phenytoin. Agents known to be highly protein bound or those with delayed metabolic effects are the best candidates for removal by TPE. Indications for TPE include progressive clinical deterioration, coma, and compromised excretory functions. Amanita poisoning is the most frequent clinical diagnosis where TPE has been utilized. Large case series showed decreased mortality among patients, mostly children, treated with TPE when compared with historical controls. Very early initiation of the treatment (less than 30 hours) resulted in the best outcomes. There are anecdotal reports on the use of immunadsorption to treat poisoning with toxins such as botulin toxin. A few case series highlighted the use of TPE to prevent limb loss in victims of snake bites.

There is increasing number of biological drugs such as monoclonal antibodies (pharmacokinetic half-life typically 10 to 30 days with potentially longer pharmacodynamic half-life) with rare but potentially serious side effects. The results of a recent study suggest that TPE may be effective in rapidly restoring CNS immune effector responses in natalizumab treated patients, which may benefit patients with serious opportunistic infections such as progressive multifocal leukoencephalopathy (PML) caused by reactivation of the polyomavirus JC.

Technical notes

The replacement fluid chosen should be one that contains enough protein to draw toxin into the blood compartment for elimination; albumin is such an agent and generally acts as an effective replacement fluid. However, some toxic substances may bind to other plasma constituents preferentially over albumin. For example, dipyridamole, quinidine, imipramine, propranolol, and chlorpromazine are known to have strong affinity for alpha-1-acid glycoprotein; for overdoses of these agents, plasma may be a more appropriate choice. Some venoms also cause coagulopathy, in which case the use of plasma should be considered.

Volume treated: 1 to 2 TPV	**Frequency:** daily
Replacement fluid: albumin; plasma	

Duration and discontinuation/number of procedures

TPEs are usually performed and continued on a daily basis until the clinical symptoms have abated and delayed release of toxin from tissues is no longer problematic.

References: mushroom poisoning [492,493]; snake venoms [494–499]; monoclonal antibodies [500–504]; others [76,101,493,505]

*As of March 30, 2010 using PubMed and the MeSH search terms overdose, poisoning, toxicology, mushroom and apheresis, plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

Incidence: rare				Procedure	Recommendation	Category
				TPE	Grade 2C	III
				IA	Grade 2C	III

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
TPE	0	1 (20)	10 (97)	18 (19)	Type II-1
IA	0	0	1 (13)	0	Type III

Description of the disease

These syndromes affect approximately 1% of cancer patients and may precede the diagnosis of cancer in 50% of cases. Major syndromes are classified according to the affected central nervous system anatomy but an international workshop consensus statement called for a combination of immunohistochemistry and Western immunoblotting for proper diagnosis. *Paraneoplastic cerebellar degeneration* (PCD) may present with symptoms developing over several days in patients with small cell lung, breast, ovarian or other gynecological cancer, and Hodgkin's lymphoma. Autoantibodies reactive against Purkinje cell cytoplasm react on Western blot analysis with 34-kDa and 62-kDa Purkinje cell proteins and are referred to as ''anti-Yo'' antibodies. The onset of symptoms, including truncal and limb ataxia, dysarthria (which may be severe), and downbeating nystagmus may precede the diagnosis of cancer by months to years. *Paraneoplastic encephalomyelitis* (PEM) in patients with small cell lung cancer presents with seizures, subacute dementia and personality change (limbic encephalitis), subacute cerebellar signs and autonomic nervous system dysfunction. Autonomic (e.g. cardiac dysrhythmias) and respiratory failure, of central origin or due to neuromuscular weakness, are principal causes of death. Most patients have polyclonal IgG anti-neuronal nuclear antibodies (ANNA-1 or anti-Hu antibodies) which react with a group of proteins with apparent molecular weights of 35–40 kDa on immunoblots of human neuronal extracts. A serum anti-Hu antibody and rapidly developing symptoms of encephalomyelitis will likely lead to a diagnosis of small cell lung cancer within several months. *Paraneoplastic opsoclonus/myoclonus* (POM) is characterized by involuntary, jerky rapid vertical and horizontal eye movements (saccades), sometimes associated with ataxia or other cerebellar signs. POM occurs mostly with breast or small cell lung cancer, but a similar syndrome occurs in children with neuroblastoma. The onset is often abrupt in adults and may beaccompanied by nausea and vomiting, and then progress to truncal ataxia, generalized myoclonus, altered mental status, and sometimes to stupor and coma. Patients with POM and breast or gynecological cancer demonstrate a serum and cerebrospinal fluid (CSF) antibody called anti-Ri, also referred to as ANNA-2, that recognizes neuronal proteins of 55 and 80 kDa on Western blots. *Paraneoplastic Stiff-Person Syndrome*, associated with antibodies to the 128 kDa synaptic vesicle-associated protein amphiphysin. *Cancer-associated retinopathy* (CAR) consists of subacute vision loss, photosensitivity, night blindness and impaired color vision. It is associated with small cell lung cancer, cervix carcinoma and malignant melanoma. Most patients have serum autoantibodies to the retinal photoreceptor protein recoverin. A large number of additional antibodies associated with paraneoplastic syndromes of the central and peripheral nervous systems and the neuromuscular junction have been described and extensively reviewed.

Current management/treatment

Although considered autoimmune, neither immunosuppressive nor anti-tumor therapy is beneficial in most cases of central nervous system (CNS) paraneoplastic neurological syndromes. Adults with POM may improve spontaneously or following corticosteroid or specific anti-cancer treatment. Neurological improvement or worsening may correlate with tumor response or relapse. Some patients with CAR may improve or stabilize with corticosteroid treatment. Intravenous immune globulin (0.5 g/kg/day for 5 days every 4 weeks for 3 months, followed by 0.5 g/kg one day per month for another 3 months) may result in improvement in patients with anti-Hu or anti-Yo, mostly in those whose symptoms are restricted to the peripheral nervous system. Aggressive immunosuppression early in the course is recommended in patients who are identified prior to a tumor diagnosis or whose tumors do not yet require specific anti-cancer therapy.

Rationale for therapeutic apheresis

The association of these syndromes with specific CSF and serum antibodies led to the use of immunosuppressive therapy, including therapeutic plasma exchange (TPE), in their management. Most patients treated with TPE have also received immunosuppressive drugs as well as specific anti-cancer therapy. TPE often lowers serum but not CSF antibodies and few patients have had convincing improvement after TPE. If a patient presents prior to development of severe neurological impairment but with a rapidly developing syndrome, aggressive immunosuppression, including TPE may be reasonable in an attempt to halt the process. Patients with acquired neuromyotonia and antibodies directed against voltage-gated potassium channels, or PCD with anti-Tr antibodies may be more likely to respond to plasma exchange. A series of 13 patients with POM or PCD were treated with staphylococcal protein A immunoadsorption of plasma. There were 3 complete and 3 partial neurological remissions. All subsequently relapsed.

Technical notes

TPE cannot be considered standard therapy for autoimmune paraneoplastic neurologic syndromes. Protein A immunoadsorption, either ''on-line'' or ''off-line'' may be employed, particularly for POM, although there is very little published experience.

Volume treated: TPE: 1 to 1.5 TPV
Protein A Immunoadsorption: 500 to 1000 ml of plasma
Replacement fluid: albumin; albumin/saline

Frequency: TPE: daily or every other day
Protein A Immunoadsorption: twice weekly

Duration and discontinuation/number of procedures:

TPE: 5 to 6 procedures over up to 2 weeks
Protein A immunoadsorption: twice weekly for 3 weeks.

References [506–542]

*As of September 4, 2009 using PubMed and the MeSH search terms Paraneoplastic Syndromes and apheresis for journals published in English language. References of the identified articles were searched for additional cases and trials.

PARAPROTEINEMIC POLYNEUROPATHIES

Incidence: MGUS: up to 3% of general population over 50 years old	Procedure	Recommendation	Category
Multiple myeloma: 4-6 per 100,000/year	TPE	Grade 1B	I (a)
	TPE	Grade 1C	I (b)
	TPE	Grade 2C	III (c)
	IA	Grade 2C	III (a, b)

# of reported patients*: 100-300

	RCT	CT	CS	CR	Type of evidence
TPE (a)	1 (39)#	0	3 (29)	1 (1)	Type I
TPE (b)	1 (39)#	0	6 (102)	3 (3)	Type I
TPE (c)	0	0	1 (4)	1 (1)	Type III
IA (a,b)	0	0	1 (3)	4 (5)	Type II-3

(a) Demyelinating polyneuropathy with IgG/IgA; (b) Polyneuropathy with IgM (±Waldenström's macroglobulinemia; ± anti-MAG); (c) Multiple myeloma with polyneuropathy; # - the same trial (see text).

Description of the disease

Polyneuropathy can present as acute, subacute, or chronic process with initial sensory symptoms of tingling, prickling, burning or bandlike dysesthesias in the balls of the feet or tips of the toes. These are usually symmetric and graded distally. Nerve fibers are affected according to axon length, without regard to root or nerve trunk distribution (e.g. stocking-glove distribution). The polyneuropathies are diverse in timing, severity, mix of sensory and motor features, and presence or absence of positive symptoms.

Polyneuropathy can be associated with and/or caused by the presence of monoclonal proteins in conditions such as amyloidosis, POEMS syndrome, Castleman's disease, type II cryoglobulinemia (see Cryoglobulinemia fact sheet), multiple myeloma (MM), B-cell lymphoma, chronic lymphocytic leukemia (CLL), Waldenström's macroglobulinemia (WM) and with IgA, IgG or IgM monoclonal gammopathy of undetermined significance (MGUS). MGUS is defined as serum monoclonal protein <3 g/dL, bone marrow plasma cells <10%, and absence of end-organ damage (e.g. lytic lesions, anemia, hypercalcemia, or renal failure).

The paraproteinemic polyneuropathies (PP) are chronic progressive illnesses and resemble chronic inflammatory demyelinating polyneuropathy (CIDP). The diagnosis can be established based on electrophysiological studies and the presence of monoclonal proteins. PP are most commonly seen in the setting of MGUS, especially IgM-MGUS. In 50% of IgM-MGUS, the specificity of IgM is myelin glycoprotein (MAG). This specificity has also been seen in WM, CLL, IgG- and IgA-MGUS. Symptoms tend to progress more rapidly in patients with IgM compared to IgA- or IgG-MGUS. The pathologic activity of anti-MAG can be transferred to laboratory animals. The monoclonal proteins damage peripheral nerves causing vasculitis (i.e. cryoglobulinemia) or protein deposition (i.e. amyloidosis).

Current management/treatment

Response to immunopressive drugs varies. Corticosteroids alone tend to be more effective in IgG- and IgA- polyneuropathies with a response rate of 40 to 60%. Combination therapy with low dose cyclophosphamide and prednisone given monthly over 6 months improves clinical outcome irrespective of antibody specificity or class. Polyneuropathies with IgG monoclonal protein resistant to this treatment have been successfully treated with cyclosporine A and carmustine. IVIG at 0.4 g/kg for 5 days has shown clinical benefit in approximately one third of the patients. However, this was not confirmed in a small randomized trial and when compared to interferon alpha. Polyneuropathies associated with MM or POEMS syndrome are difficult to treat and may respond to alkylating agents. Response, if it occurs, is typically slow. Recent reports with limited number of patients showed that anti-CD20 antibody (rituximab) has been successful in IgM PP with anti-MAG. Some patients with anti-MAG neuropathy also have benefited from fludarabine or cladribine. These new therapies are likely to change the therapeutic approach if the benefits are confirmed in larger trials.

Rationale for therapeutic apheresis

A randomized, double-blind trial compared plasma exchange to sham plasma exchange in 39 patients with stable or worsening MGUS-associated polyneuropathy. TPE was performed twice a week for three consecutive weeks. In the IgG and IgA MGUS group there was a neurological improvement as measured by neuropathy disability score, weakness score, and summed compound muscle action potential. While some measures did not reach statistical significance, the observed differences were clinically significant. Importantly, patients from the sham group who were later crossed to TPE treatment also improved clinically. The clinical response lasted from 7 to 20 days without any additional treatment. The IgM MGUS group did not appear to respond to TPE in this trial. The heterogeneity of the IgG group, which included patients with more treatment refractory axonal neuropathy, may have adversely affected the observed results. A retrospective analysis of 19 patients with IgM and 15 patients with IgG PP concluded that the two groups were equally likely to respond to plasma exchange or other therapies. Patients with CIDP and MGUS respond well to TPE. In a small study, patients with PP and IgM paraproteins with anti-MAG activity responded to five to seven monthly courses of TPE combined with IV cyclophosphamide. Similar results were observed in patients with anti-GM1 antibodies.

Other TA modalities such as double filtration plasmapheresis and Staphylococcal protein A silica immunoadsorption may be effective alternatives to conventional TPE in PP though clinical experience is limited.

Technical notes

Patients with demyelinating PP may be treated at any time in their course (including patients referred up to 4 years after onset of symptoms).

Volume treated: 1 to 1.5 TPV	**Frequency:** every other day
Replacement fluid: albumin; plasma	

Duration and discontinuation/number of procedures

The typical course is 5 to 6 treatments over the course of 10 to 14 days. Long term TPE or slow tapering off TPE can be considered. The patient may continue to improve over weeks following cessation of plasma exchange. If the level of paraprotein is correlative to the polyneuropathy then it can be monitored to evaluate the frequency of treatment. However, the titer of the paraprotein may not correlate with the clinical disease state.

References [56,543–555]

*As of January 30, 2010 using PubMed and the MeSH search terms polyneuropathy, apheresis, plasma exchange, plasmapheresis, anti-MAG, paraproteinemic polyneuropathy, and MGUS for articles published in the English language. References of the identified articles were searched for additional cases and trials.

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS AND SYDENHAM'S CHOREA

Incidence: unknown for PANDAS and SC; 1.5-2.5 % and 6.6-24% of school-aged children and adolescents have obsessive compulsive disorders (OCD) and tic disorders, respectively	Procedure	Recommendation	Category
	TPE (PANDAS)	Grade 1B	I (exacerbation)
	TPE (SC)	Grade 1B	I

# of reported patients*: <100

	RCT	CT	CS	CR	Type of evidence
PANDAS	1 (29)	0	0	4 (4)	Type I
SC	1 (18)	0	0	0	Type I

Description of the disease

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and Sydenham's Chorea (SC) are pediatric post-infectious autoimmune neuropsychiatric disorders. Both share an array of neuropsychiatric symptoms, which typically follow Group-A beta-hemolytic streptococcus (GABHS) infection. Both may have a shared etiopathogenesis. Some investigators have reported that antibodies produced against GABHS, especially streptococcal M-proteins, cross-react with neurons of the basal ganglia. GABHS infection has been associated with childhood-onset neuropsychiatric disorders in genetically susceptible individuals, such as SC, PANDAS, OCD, tic disorder, Tourette's syndrome, etc. A subgroup of these disorders is identified by the acronym PANDAS, which was first described in 50 children by Swedo et al in 1998. The five diagnostic criteria for PANDAS include: 1) presence of OCD and/or a tic disorder, 2) prepubertal onset, 3) episodic course with abrupt onset or symptom exacerbations, 4) a temporal association of symptoms with GABHS infection and 5) association with neurological abnormalities (motoric hyperactivity or choreiform movements). The onset of PANDAS is acute and abrupt, often associated with co-morbid neuropsychiatric symptoms, including mood lability, attention deficit-hyperactivity disorder, oppositional defiant disorder, overanxious disorder, separation anxiety, tactile/sensory defensiveness, enuresis, and catatonia. Severe symptoms often last several weeks to months or longer and then gradually subside. SC, a neuropsychiatric manifestation of rheumatic fever, occurs in about 10-20% of patients with acute rheumatic fever, typically 4-8 weeks after a GABHS pharyngitis. The major clinical manifestations include chorea, hypotonia and emotional lability. SC is self-limiting and resolves after 6-9 months, but up to 50% of cases have persistence and recurrence of symptoms. SC is characterized by rapid, jerky, involuntary muscle contractions of the limbs, face, and trunk. During the choreic episode, more than 60% of children with SC have OCD. The mean ages of onset for PANDAS and SC are 6.8 years old (3-12) and 8.4 years old (5-15), respectively, with male predominance in PANDAS (2.6:1) and female predominance in SC (2:1). No laboratory tests that are specific for diagnosis and differentiation of PANDAS and SC. Evidence of GABHS infection through throat culture and/or an elevated or increasing antistreptococcal antibody titer [(e.g., anti-streptolysin O (ASO), anti-deoxyribonuclease–B (antiDNAse-B)] supports the diagnosis of both. Elevated levels of antineuronal antibodies and/or anti-basal ganglia antibodies have been reported in both. MRI studies demonstrated striatal enlargement in basal ganglia, especially in caudate, putamen, and globus pallidus in both. SC is diagnosed exclusively by the presence of chorea and a history of rheumatic fever. In PANDAS, exacerbations of symptoms, at least two episodes of neuropsychiatric symptoms, are temporarily associated with streptococcal infection but is not associated with rheumatic fever. None of 60 children with PANDAS had rheumatic carditis by ECHO. During times of remission, a negative throat culture or stable titers are noted. It is very important to differentiate the two since their treatment can be different. In addition, application of all five criteria to make a diagnosis of PANDAS would prevent unwarranted use of antibiotics in children with OCD or tics.

Current management/treatment

Initial treatments for PANDAS include cognitive behavioral therapy and/or anti-obsessional medications. Prompt antibiotic administration is indicated in patients with PANDAS with a tonsillo-pharyngitis and a positive GABHS throat culture. In a double blind, randomized controlled trial, penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and symptom exacerbations in 23 children with PANDAS. This study suggested that penicillin prophylaxis might be considered in children with PANDAS and who have ongoing risk of GABHS exposure. However, azithromycin prophylaxis should not routinely be recommended because of emerging resistant streptococci. Tonsillectomy may represent an effective prophylactic treatment option in PANDAS patients, if clinically indicated. Severe form of SC is treated with diazepam, valproic acid, carbamazepine, or haloperidol. If these fail, corticosteroids may be tried. Unlike in PANDAS, children with SC require long-term penicillin prophylaxis to reduce the risk of rheumatic carditis. In severely symptomatic patients with PANDAS or SC, immunomodulatory therapies, such as intravenous immunoglobulin (1 g/kg/day for 2 days) or TPE, have been shown to be effective in reducing symptom severity or shorten the course.

Rationale for therapeutic apheresis

Because of the possible role of antineuronal antibodies in the pathogenesis, antibody removal by TPE may be effective. However, the mechanism for the benefit of TPE is not clear, as there is a lack of relationship between therapeutic response and the rate of antibody removal. In two patients with PANDAS, TPE resulted in significant and rapid improvement of OCD symptom and a simultaneous decrease in basal ganglia swelling on MRI. A randomized placebo-controlled trial of IVIG and TPE on 29 children with PANDAS showed that both therapies at one month after treatment produced striking improvements in OCD, with mean improvement of 45% and 58%, respectively, as well as improvement in anxiety and overall functioning. More than 80% of the patients who received IVIG or TPE remained much or very much improved at 1 year. The TPE group appeared to have greater OCD and tic symptom relief than did the IVIG group. Another randomized controlled study on 18 patients with SC showed that the mean chorea severity scores decreased by 72%, 50%, and 29% in the IVIG, TPE, and the prednisone groups, respectively.

Technical notes

When TPE is performed every other day, PT, PTT and fibrinogen level must be monitored. FFP can be supplemented as a part of replacement fluid to maintain fibrinogen level above 100 mg/dL at a dose of 10-15 mL of FFP/kg.

Volume treated: 1 to 1.5 TPV	**Frequency:** every other day
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

Five or 6 procedures over 7 to 14 days were utilized in the RCT. There are no data on any benefit of repeated treatment.

References [451,556–576]

*As of December 31, 2009 using PubMed and the MeSH search terms: PANDAS, Sydenham's chorea, neuropsychiatric disorder, obsessive-compulsive disorder, tics, basal ganglia disease, streptococcal infection, plasma exchange, plasmapheresis, for articles published in the English language. References of the identified articles were searched for additional cases and trials.

PEMPHIGUS VULGARIS

Incidence: 0.42 per 100,000/year in the US	Procedure	Recommendation	Category
	TPE	Grade 2B	IV
	ECP	Grade 2C	III

# of reported patients*: 100-300

	RCT	CT	CS	CR	Type of evidence
TPE	1 (40)	0	8 (87)	13 (13)	Type I
ECP	0	0	1 (4)	6 (10)	Type III

Description of the disease

Pemphigus vulgaris is a rare, potentially fatal, autoimmune mucocutaneous blistering disease. Both genders are equally affected with the mean age of onset in the sixth and seventh decade of life. The patients present with skin lesions typically flaccid blisters which can be recurrent and relapsing. The blisters can be located on the entire body surface as well as on the mucous membranes of the mouth. The lesions tend to peel superficially or detach easily. A large surface of skin can be affected at any given point leading to situations akin to severe burn. Pathology of pemphigus vulgaris is characterized by the in vivo deposition of an autoantibody on the keratinocyte cell surface. This antibody, which is also present in the circulation, is typically directed against a 130-kDa protein (desmoglein 3). Additional autoantibodies against desmoglein 1 have been detected. Histology reveals the presence of a suprabasilar intraepidermal split with acantholysis. There are deposits of IgG and C3 on the corticokeratinocyte cell surface in the mid and lower or entire epidermis of perilesional skin or mucosa. In some reports titers of IgG4 antikeratinocyte antibodies correlated with disease activity.

Current management/treatment

The treatment of pemphigus vulgaris, especially in its severe form, is challenging. Historically, this disease was associated with a high morbidity and mortality. Introduction of corticosteroids reduced the mortality rate from 70 to 100% to a mean of 30%. However, long-term administration of high doses of corticosteroids can be associated with severe adverse effects (e.g., hypertension, osteoporosis, atherosclerosis, peptic ulcer disease, aseptic necrosis, diabetes mellitus/glucose intolerance, and immunosuppresion). Other therapeutic options include dapsone, gold, and systemic antibiotics. They are often used in combination with other immunosuppressant agents such as azathioprine, methotrexate, and cyclophosphamide. Recently newer therapeutic modalities such as mycophenolate mofetil, chlorambucil, dexamethasone-cyclophosphamide pulse therapy, cyclophosphamide, TPE, extracorporeal photochemotherapy (ECP), intravenous immunoglobulin (IVIG) therapy, and rituximab, anti-CD20 monoclonal antibody, have been investigated. The combination of IVIG and anti-CD20 antibody have been found effective in a case series of 11 patients with refractory disease. In addition, some newer experimental technologies involve cholinergic receptor agonists, desmoglein 3 peptides and a p38 mitogen activated protein kinase inhibitor.

Rationale for therapeutic apheresis

The rationale for using TPE in the treatment of pemphigus vulgaris is based on the presence of circulating pathogenic autoantibodies. TPE has been utilized in patients with severe symptoms who either received high doses of conventional agents and/or had an aggressive and rapidly progressive disease. TPE was used in patients in all age groups (13–80 years old). The duration of disease prior to using TPE ranged between 1 month and 25 years. All reported patients have received high-dose systemic corticosteroids and immunosuppressive agents which either produced life-threatening adverse effects or failed to control the disease. The goal of TPE was to reduce the level of autoantibodies with subsequent improvement in clinical symptoms. In one small multicenter randomized control trial patients were randomized into prednisolone alone (n=18) and prednisolone plus 10 large volume TPE (n=22) over four weeks. There were four septic deaths in the TPE arm. There was no steroid sparring effect noted in the TPE arm. The patients received significant doses of prednisolone (control arm 4246 ± 1601 mg vs 5237 ± 5512 mg in the TPE arm). The study, though not powered to answer the question of clinical benefit, underlines the potential side effects of immunosuppressive therapy.

Technical notes

The TPE protocols used in pemphigus vulgaris vary widely and have been usually based on the observed clinical response after each treatment. The reported volume processed was as low as 400 mL and as high as 4,000 mL and the reported frequency of treatments varied widely as well. Though, more recent reports noted that one plasma volume exchanges are preferable in patients who are resistant to conventional therapy. The levels of autoantibody have been noted to rebound in the reported patients within 1–2 weeks after discontinuation of treatment which necessitates continuation of immunosuppression. The clinical response in patients who underwent ECP was observed after two to seven cycles (two daily procedures per cycle). The total number of received cycles varied from 2 to 48. In one report 100% clinical response with decreased autoantibody titer was reported. The follow-up ranged between 4 and 48 months. The disease was controlled in most patients, but only two patients were able to discontinue all oral systemic agents.

Volume treated: TPE: 1 to 1.5 TPV; ECP: An MNC product of 200 - 270 mL. The two step process method collects and treats MNCs obtained from 2-times TBV processing. **Replacement fluid:** TPE: albumin, plasma; ECP: not applicable;	**Frequency:** TPE: daily or every other day; ECP: two consecutive days (one series) every 2 or 4 weeks

Duration and discontinuation/number of procedures

For plasma exchange, as noted above, the treatment protocols are highly variable. The rational approach should include monitoring of autoantibody titers and clinical symptoms. The lack of clinical response after a trial period with concomitant adequate immunosuppression should be sufficient to discontinue treatment.

For ECP, the treatments were continued until clinical response was noted. The rational discontinuation criteria should be similar to those for TPE.

References [227,577–587]

*As of November 6, 2009 using PubMed and the MeSH search terms pemphigus vulgaris and apheresis and plasmapheresis and photopheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

PHYTANIC ACID STORAGE DISEASE (REFSUM'S DISEASE)

Incidence: rare			Procedure	Recommendation	Category
			TPE	Grade 2C	II

# of reported patients*: <100

RCT	CT	CS	CR	Type of evidence
0	0	2 (12)	3 (3)	Type II-3

Description of the disease

Phytanic Acid Storage disease (Refsum's Disease), also known as heredopathia atactica polyneuritiformis, is an autosomal recessive disorder first described by Sigvald Refsum, a Norwegian neurologist, in 1946. Patients have significant defects in the metabolism of phytanic acid (PA) due to deficiency in alpha-oxidase. This branched chain fatty acid is derived exogenously from dietary sources. The inability to degrade PA results in its accumulation in fatty tissues, liver, kidney, myelin, lipoproteins, and the plasma. Clinical consequences are largely neurological including retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, sensorineural deafness and anosmia. Other manifestations include skeletal abnormalities, cardiac arrhythmia and ichthiosis. The clinical progression is typically slow and gradual with onset of signs and symptoms during the 2nd or 3rd decades of life due to the gradual accumulation of phytanic acid from dietary sources. The most frequent earliest clinical manifestations are night blindness and visual disturbances. Progression of symptoms can lead to retinitis pigmentosa, and possibly loss of sight. Patients with cardiac manifestation may experience arrhythmias which could be fatal or prompt cardiac transplantion. The specific biochemical basis for the accumulation of phytanic acid in these patients is related to an enzyme defect in phytanoyl-CoA hydrolase.

Current management/treatment

Limiting intake of PA by dietary restriction to 10 mg daily is the cornerstone of therapy. PA comes primarily from animal sources such as dairy, butter, cheeses, meats, and some fish. Diet alone can benefit many patients and lead to reversal of neuropathy, weakness and icthiosis. Care is taken to maintain overall general nutrition and caloric intake to avoid rapid weight loss which has precipitated clinical relapse due to sudden mobilization of PA from liver and adipose tissue stores. The relative unpalatability of diets low in PA limits compliance with, and thus the effectiveness of, dietary management of this disorder. Even with adequate dietary compliance, there can be a delay in the fall of PA levels presumably because of its release from adipose tissue stores.

Rationale for therapeutic apheresis

TPE rapidly reduces plasma PA in the setting of acute attacks or exacerbation of the disease as well as for maintenance therapy. The normal plasma PA level in humans is <33 μmole/L. Symptomatic levels of PA in Refsum's Disease range from 700 to 8000 μmole/L. A number of small case series and isolated reports have described clinical improvements in patient signs and symptoms with plasma exchange in conjunction with dietary control. TPE has been found to improve the polyneuropathy, ichthyosis, ataxia, and cardiac dysfunction in most but not all patients treated. Unfortunately, as is also reported with dietary treatment alone, the visual, olfactory, and hearing deficits do not respond. Patients may experience severe exacerbations of disease during episodes of illness or weight loss, such as during the initiation of dietary management. PA levels increase dramatically, possibly due to mobilization of PA stored in adipose tissue. Most authors have used TPE to treat such episodes with marked rapid improvement in symptoms. Chronic TPE strategies have been described which attempt to deplete PA stores following initiation of dietary therapy or to allow for less restrictive diets. Since PA is also bound to plasma lipoproteins and triglycerides, lipapheresis using cascade filtration been used to successfully manage these patients.

Technical notes

Although approaches to therapeutic apheresis for Refsum's Disease vary, a typical course consists of 1-2 plasma exchange treatments per week for several weeks to month. In some cases maintenance plasma exchanges continue with decreasing frequency over subsequent weeks to months.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

Therapeutic strategy is ultimately determined by monitoring the patient's PA level, clinical signs and symptoms, and the need to control or prevent exacerbations of the disease.

References [508–602]

*As of December 30, 2009 using PubMed and the MeSH search terms Refsum's or phytanic acid and apheresis, plasma exchange, or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

POLYCYTHEMIA VERA AND ERYTHROCYTOSIS

	Procedure	Recommendation	Category
Incidence: 0.02-2.8/100,000 per year for polycythemia vera (PV)	Erythrocytapheresis	Grade 2C	III (PV)
Prevalence: 22/100,000 (PV) and 0.3% secondary erythrocytosis	Erythrocytapheresis	Grade 2B	III (secondary erythrocytosis)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
Polycythemia vera	0	0	4 (434)	0	Type II-3
Secondary erythrocytosis	0	1 (98)	4 (175)	1 (1)	Type II-1

Description of the disease

Absolute erythrocytosis is defined as a red cell mass of at least 25% above the gender-specific mean predicted value. Hematocrit (Hct) values > 60% for males and >56% for females are always indicative of absolute erythrocytosis, as these levels cannot be achieved with plasma volume contraction alone or other causes of ''apparent'' or ''relative'' erythrocytosis. Primary erythrocytosis refers to the myeloproliferative condition polycythemia vera (PV), in which an abnormal hematopoietic stem cell clone autonomously overproduces red cells. Additional features of PV include splenomegaly, granulocytosis, thrombocytosis and a point mutation in the nonreceptor tyrosine kinase *JAK2* gene. Secondary erythrocytosis refers to isolated red cell overproduction due to a congenital erythropoietic or hemoglobin defect, chronic hypoxia related to a respiratory or cardiac disorder, ectopic erythropoietin (Epo) production (e.g. from renal cell carcinoma, uterine leiomyoma), Epo augmentation (e.g. postrenal transplantation) or without a primary disorder or features of PV (i.e. idiopathic erythrocytosis). Whole blood viscosity increases significantly as the Hct level exceeds 50%. Patients with PV may experience hyperviscosity-related symptoms with modestly elevated Hct, whereas patients with secondary erythrocytosis are usually asymptomatic until Hct levels exceed 55-60%. Hyperviscosity complications include headache, dizziness, slow mentation, confusion, fatigue, myalgia, angina, dyspnea and thrombosis. Roughly 15-40% of patients with PV develop arterial or venous thrombosis. Thrombotic risk factors with PV include uncontrolled erythrocytosis (Hct >55%), age >60 years, history of prior thrombosis, cardiovascular comorbidities, immobilization, pregnancy and surgery. PV may also induce microvascular ischemia of the digits or in the central nervous system.

Current management/treatment

Erythrocytosis and hyperviscosity symptoms due to pulmonary hypoxia resolve with long-term supplemental oxygen and/or continuous positive airway pressure maneuvers. Surgical interventions may correct secondary erythrocytosis due to a cardiopulmonary shunt, renal hypoxia or an Epo-producing tumor. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are beneficial for postrenal transplantation erythrocytosis. When the primary disorder cannot be reversed, symptomatic hyperviscosity can be treated by isovolemic phlebotomy. The therapeutic endpoint for phlebotomy varies according to the underlying etiology and the need for an increased oxygen-carrying capacity (especially with cyanotic congenital heart disease). Patients with PV routinely undergo phlebotomies to maintain a normal Hct (i.e. <45%); chronic phlebotomies result in iron deficiency, which decreases red cell overproduction. Low-dose aspirin is useful for thromboprophylaxis. Cytoreductive agents, such as hydroxyurea, may be indicated to control the Hct and/or platelet count.

Rationale for therapeutic apheresis

Red cell reduction by automated apheresis (erythrocytapheresis), like isovolemic phlebotomy, corrects hyperviscosity by lowering the Hct, which reduces capillary shear rates, increases microcirculatory blood flow and improves tissue perfusion. Optimal tissue oxygenation minimizes the release of prothrombotic factors induced by ischemia. For PV patients with acute thromboembolism, severe microvascular complications or bleeding, therapeutic erythrocytapheresis may be a useful alternative to emergent large-volume phlebotomy; particularly if the patient is hemodynamically unstable. Erythrocytapheresis may also be appropriate prior to surgery to reduce the high risk of perioperative thrombohemorrhagic complications in a PV patient with high Hct (>55%). Plateletapheresis as well as erythrocytapheresis may be indicated for patients with PV and an acute complication associated with uncontrolled thrombocytosis and erythrocytosis. With secondary erythrocytosis and symptomatic hyperviscosity or thrombosis, red cell reduction by apheresis may, in selected cases with circulatory overload, be a safer and more effective approach than simple phlebotomy. One case control study of 98 patients with PV (n=6) or secondary erythrocytosis (n=92) observed that chronic automated erythrocytapheresis allowed significantly greater treatment intervals (median 135-150 days; range 2-7 months) compared to chronic phlebotomy (median 40 days; range 20-60 days). This same benefit has been reported in several case series using automated erythrocytapheresis.

Technical notes

Automated apheresis instruments can calculate the volume of blood needed to remove to achieve the desired post-procedure Hct. Saline boluses may be required during the procedure to reduce blood viscosity in the circuit and avoid pressure alarms.

Volume treated: volume of blood removed is based on the total blood volume, starting Hct and desired post-procedure Hct. **Replacement fluid:** albumin/saline	**Frequency:** as needed for symptomatic relief or to reach desired Hct (usually one)

Duration and discontinuation/number of procedure

In patients with PV, the goal is normalization of the Hct (i.e. <45%). For secondary erythrocytosis, the goal is to relieve symptoms but retain a residual red cell mass that is optimal for tissue perfusion and oxygen delivery. A post-procedure Hct of 50-52% might be adequate for pulmonary hypoxia or high oxygen affinity hemoglobins, whereas Hct values of 55-60% might be optimal for patients with cyanotic congenital heart disease. A single procedure should be designed to achieve the desired post-procedure Hct.

References [334,603–612]

*As of October 15, 2009 using PubMed and the MeSH search terms erythrocytosis, polycythemia vera, erythrocytapheresis, apheresis, hyperviscosity, myeloproliferative disorder and myeloproliferative neoplasm for reports published in the English language. References of the identified articles were searched for additional cases and trials.

POST TRANSFUSION PURPURA

Incidence: 2 per 100,000/year				Procedure TPE	Recommendation Grade 2C	Category III

# of reported patients*: < 100					
RCT	**CT**	**CS**	**CR**	**Type of evidence**	
0	0	1 (3)	15 (23)	Type II-3	

Description of the disease

Post Transfusion Purpura (PTP) is characterized by severe and abrupt onset of profound thrombocytopenia (often $<10 \times 10^9$/L) 5 to 10 days after transfusion of any blood component. PTP occurs most commonly in patients whose platelets lack the HPA-1a antigen and they have preformed alloantibodies against HPA-1a due to immunization during pregnancy or blood transfusion. It is not clearly understood why sudden thrombocytopenia develops after transfusion of, in most cases, red cells in patients with HPA-1a negative platelets. The most plausible explanation is that the soluble HPA-1a antigen or platelet microparticles carrying HPA-1a present in the transfused blood component gets adsorbed to GPIIIa on the patient's platelets. This induces an anamnestic response and these alloantibodies then destroy the patient's own platelets that have adsorbed the antigen. Immune-mediated destruction of antigen negative platelets can be described as bystander immune cytolysis. Other hypotheses include immune complex mediated destruction of platelets and autoantibody phenomenon, both of which are poorly supported by the evidence. The detection of antibodies (generally high titer) against HPA-1a antigen in a patient's serum that lacks this antigen is necessary for the diagnosis of PTP. The high titer antibody can be detected for up to one year after the PTP episode. PTP is self-limited, with complete recovery in even untreated patients in about 20 days. The mortality of PTP is 10 to 20%. Sometimes, especially after cardiac surgery, PTP patients can be falsely diagnosed as heparin-induced thrombocytopenia (HIT) in the early stages. One distinction, however, is that a platelet count of $<20 \times 10^9$/L is uncommon in HIT and patients do not bleed.

Current management/treatment

The current mainstay of the treatment for PTP is a high dose intravenous immunoglobulin (IVIG; 0.4g/kg/day for 2 to 5 day or 1 g/kg/day for 2 days). IVIG possibly acts by Fc receptor blockade of the reticuloendothelial system. All nonessential transfusions of blood components should be immediately discontinued. A bleeding patient should be transfused with HPA-1a negative platelets, if available. HPA-1a positive platelet transfusion is generally ineffective and likely to stimulate more antibody production. Patients are also given high dose of corticosteroids. TPE is indicated only if IVIG is not effective and severe thrombocytopenia persists. Recombinant FVIIa (Novoseven®) may be considered in a bleeding patient when HPA-1a negative platelets are not available.

Rationale for therapeutic apheresis

Removal of HPA-1a alloantibodies by TPE decreases the antibody titer and removes unabsorbed HPA-1a antigen; thereby, increasing platelet survival and reversing the bleeding risk. TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIG therapy is not effective.

Technical notes

Due to severe thrombocytopenia, the AC ratio should be adjusted accordingly. Typically the replacement fluid is albumin to avoid further exposure to HPA-1a antigen. However, in bleeding patient plasma supplement can be given toward the end of procedure (e.g. albumin:plasma volume ratio of 75:25).

Volume treated: 1 to 1.5 TPV	**Frequency:** daily
Replacement fluid: albumin; plasma	

Duration and discontinuation/number of procedures

TPE can be discontinued when platelet count starts increasing ($>20 \times 10e9$/L) and non-cutaneous bleeding stops.

Reference [126,613–618]

*As of November 8, 2009 using PubMed and the MeSH search terms post transfusion purpura and apheresis for articles published in the English language. References in identified articles were searched for additional cases and trials.

RED CELL ALLOIMMUNIZATION IN PREGNANCY

Incidence: 100 per 100,000 newborns/year in the US				**Procedure**	**Recommendation**	**Category**
				TPE	Grade 2C	II (prior to IUT availability)

# of reported patients*: >300

RCT	**CT**	**CS**	**CR**	**Type of evidence**
0	1 (57)	12 (250)	20 (22)	Type II-3

Description of the disease

Hemolytic disease of the fetus and newborn (HDFN, also term erythroblastosis fetalis or hemolytic diseae of the newborn) occurs when maternal plasma contains an alloantibody against a red blood cell (RBC) antigen carried by the fetus. The maternal IgG crosses the placenta and causes hemolysis of the fetal RBCs. This leads to fetal anemia and when severe enough, fetal death (hydrops fetalis). Most frequently HDFN is secondary to anti-D (previously termed Rh disease) but it can be caused by a variety of RBC alloantibodies (anti-K, anti-C, anti-PP1Pk, and anti-E, for instance). Sensitization to RBC antigens usually occurs after fetomaternal hemorrhage during pregnancy or delivery, or through previous RBC transfusion. Only 0.1 mL of fetal RBCs can result in Rh sensitization. Due to the routine use of prophylactic Rh immunoglobulin during pregnancy and post-partum, the incidence of HDFN secondary to anti-D has greatly decreased. The severity of HDFN usually increases with subsequent pregnancies.

Current management/treatment

The management of a pregnant woman with a newly identified clinically significant alloantibody is as follows. First, take a history to help identify the source of exposure, such as previous pregnancy or transfusion. Second, phenotype the fetus' father to assess for risk of HDFN, if paternity is assured. If the father does not carry the RBC antigen, then no further work up needs to be performed. If the father is heterozygous for the antigen, the fetus has a 50% chance of also expressing the antigen and being at risk. If the father is homozygous for the antigen, the fetus is at risk. Third, maternal antibody titer should be performed. For the majority of antibodies (see anti-K below), the higher the titer, the more severe HDFN. Titers should be repeated with every scheduled prenatal obstetrics visit (approximately monthly until 24 weeks and then every 2 weeks until term). Fourth, if titers, performed in the same laboratory, are above 16 or have increased 4 fold from the previous sample, ultrasound and/or amniocentesis should be performed to evaluate the fetus. Ultrasound can detect signs of anemia (middle cerebral artery blood flow velocity) or hydrops (ascites) and is a non-invasive method of following the severity of HDFN. Amniocentesis provides samples for fetal genotype (if needed), amniotic fluid spectral analysis, and fetal lung maturity assessment. The severity of HDFN after 26 weeks gestation can be predicted by spectral analysis of amniotic fluid bilirubin at 450 OD by plotting the results on the Queenan modification of the Liley's correlative graph. Results in the severe zone or high moderate zone indicate need for fetal blood sampling, delivery, or close follow up. Fetal lung maturity testing predicts if the fetus can be safely delivered. Fetal blood sampling also allows for the measurement of fetal hematocrit to determine the need for an intrauterine transfusion (IUT), which cannot occur until about 20 weeks gestational age. IUT uses RBCs negative for the antigen against which maternal antibody is directed. Fetal mortality related to IUT is 1 to 2%. IUT can be repeated, approximately every 1 to 2 weeks, until the fetus is ready for delivery. HDFN can result in neonatal hyperbilirubinemia, which can cause kernicterus and permanent brain damage. Therefore, post delivery the neonate must be closely monitored to prevent and treat hyperbilirubinemia.

Anti-K (Kell) suppresses RBC production as well as causes hemolysis, and antibody titers and amniocentesis for delta 450 OD measurements are not as predictive as other antibodies. Thus, monitoring the middle cerebral artery blood flow velocity by ultrasound is the preferred method to monitor disease severity.

If the fetus is known to be at high risk for hydrops fetalis based on ultrasound or previous prenatal loss, a more aggressive approach early during pregnancy is warranted. The current mainstay of treatment is IUT, but if there is a high risk of fetal demise or signs of hydrops prior to 20 weeks, then intravenous immunoglobulin (IVIG) and/or plasma exchange (TPE) may be indicated.

Rationale for therapeutic apheresis

TPE removes the maternal RBC alloantibody that causes HDFN. Therefore, TPE will potentially decrease the maternal antibody titer and, in turn, the amount of antibody transferred to the fetus, thereby protecting the fetus from HDFN. Survival of the fetus in severe cases of HDFN with the use of TPE and/or IVIG prior to IUT is about 70%. Typically, IUT can be performed after the fetus reaches 20 weeks of gestation.

Technical notes

TPE can safely be performed during pregnancy. Physiologically, blood and plasma volumes increase as the pregnancy progresses. In the second or third trimester, the patient should lay on her left side to avoid compression of the inferior vena cava by the gravid uterus. Hypotension should be avoided as it may result in decrease perfusion to the fetus.

Volume treated: 1 to 1.5 TPV	**Frequency:** three procedures per week
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

TPE should be considered early in pregnancy (from 7 to 20th week) and continued until IUT can safely be administered (about 20th week of gestation). Close monitoring of the fetus for signs of hydrops will aid in guiding treatment. One approach is to use TPE for the first week (3 procedures) after the 12th week of pregnancy followed by weekly IVIG (1 g/kg) until the 20th week (Ruma et al).

References [619–626]

RENAL TRANSPLANTATION

Incidence: 6 per 100,000/year in the US; AMR 10% renal transplant recipients and 40% renal transplant recipients who underwent desensitization	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 1B	I (AMR)
	TPE	Grade 1B	II (Desensitization, living donor, positive crossmatch due to donor specific HLA antibody)
	TPE	Grade 2C	III (High PRA, cadaveric donor)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
AMR	3 (61)	8 (342)	35 (499)	13 (14)	Type I
Desensitization	0	4 (240)	28 (436)	11 (11)	Type II-2
High PRA	0	0	1 (20)	0 (0)	Type II-3

Description of the disease

Kidney transplantation is performed to allow individuals with end stage renal disease to discontinue dialysis. Transplantation increases the life span of these individuals. Barriers to transplantation include antibodies to human leukocyte antigens (HLA) and ABO incompatibility with the donor because there is an increased risk for graft loss secondary to hyperacute rejection. Patients with an elevated HLA antibody screen have difficulty finding an HLA compatible donor and remain on the transplantation list significantly longer than unsensitized patients. The goal of desensitization protocols is to allow these individuals to be transplanted using a donor kidney that would otherwise not be usable due to the high likelihood of graft loss.

Allograft rejection has traditionally focused on T cell mediated process causing cellular rejection. Antibody-mediated rejection (AMR; also termed acute humoral rejection or acute vascular rejection) has been thought of as antibody mediated based on correlating histological findings with the identification of donor specific antibody. Recently a clear histological diagnosis of AMR can be made based on the Sixth Banff Conference on Allograft pathology in 2001. The diagnosis is based on (1) documentation of donor specific antibody (DSA); (2) histologic evidence of acute tissue injury, such as acute tubular injury, neutrophils in peritubular capillaries and/or glomeruli, and/ or capillary thrombosis, or intimal arteritis/ fibrinoid necrosis/ intramural or transmural inflammation in arteries; and (3) C4d in peritubular capillaries or immunoglobulin and complement in arterial fibrinoid necrotic areas by immunohistology. AMR affects fewer than 10% of renal allografts. Recipients at higher risk include those with previous transplant and high panel-reactive antibodies.

Information about the use of plasma exchange (TPE) in ABO incompatible renal transplantation can be found in a separate fact sheet focusing on ABO incompatibility and solid organ transplantation.

Current management/treatment

New immunosuppressive drugs are continually being developed to prevent and treat acute renal allograft rejection, and to decrease antibody titers. All transplant recipients are placed on immunosuppressive therapy but individuals with a high likelihood of acute rejection, including those with HLA antibodies and recipients of cadaveric organs, receive more intense regimens. The optimal regimen has yet to be defined but include the use of cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, and antithymocyte globulin.

Published desensitization protocols use high dose intravenous immunoglobulin (IVIG), plasma exchange (TPE); or immunoadsorption and/or rituximab (anti-CD20) alone or in combination to convert a positive crossmatch to a negative crossmatch and allow for transplantation. In addition, some case series use other immunosuppressives such bortezomib (proteasome inhibitor). The TPE/IVIG regimen has been used for potential living donors while the high dose IVIG regimen has been used for both living and deceased donors, and more recently with rituximab. IVIG alone without rituximab and/or TPE has highest AMR rates. Immunosuppressive drugs, such as rituximab, glucocorticsteroids, mycophenolate mofetil, and tacrolimus, are initiated at the start of the protocol. Post transplantation rapid diagnosis and treatment of AMR is essential.

In a retrospective review comparing sensitized (positive panel reactive antibody [PRA]) versus unsensitized patients receiving crossmatch negative cadaveric kidney transplants, sensitized patients had higher rates of graft rejection and graft loss. In this study 20 out of the 73 patients received pretransplantation TPE and/or immunoadsorption (IA) and of these 10 achieved negative PRAs. Graft rejection rate was 18% in unsensitized group, 41% in non-TPE and/or IA sensitized group, and 20% in TPE and/or IA sensitized group (30% positive PRA at transplant and 10% negative PRA at transplant). Graft loss rate was 5% in unsensitized group, 21% in non-TPE and/or IA sensitized group, and 15% in TPE and/or IA sensitized group (20% positive PRA at transplant and 10% negative PRA at transplant). Therefore, pretransplant TPE and/or IA may decrease graft loss rates in highly sensitized patients receiving cadaveric transplants.

Treatment of AMR includes increasing immunosuppressive medications as well as rituximab, TPE, IVIG, splenectomy. In severe cases or cases refractory to TPE+IVIG, splenectomy and rituximab have been used. Clinical trials have demonstrated improved graft survival with TPE/IVIG versus TPE alone or IVIG alone, and TPE + rituximab versus TPE alone.

The use of rituximab has been associated with increased rates of infection.

Rationale for therapeutic apheresis

In antibody-mediated rejection DSA are generated after transplantation. These antibodies can be removed with plasma exchange, double filtration plasmapheresis, lymphoplasmapheresis, and immunoabsorbtion. Therapeutic apheresis is always in combination with other immunosuppressive drugs, such as antithymocyte globulin glucocorticosteroids, rituximab, and intravenous immunoglobulin. Randomized controlled trials in the early 1980s did not show plasma exchange to be beneficial when uses in combinations with corticosteroids for either acute rejection with DSA detected or acute vascular rejection. Case series since 1985 have shown improvement when plasma exchange is used in patients with acute vascular rejection in combination with a variety of anti-rejection medications. This is likely due to improved anti-rejection medications, improved detection of DSA, and improved definition of AMR using the Banff criteria. Previously there was a high graft loss rate with acute vascular rejection; current regimens which include TPE have a graft survival rate of 70 to 80% (90% in reports with TPE, IVIG, and rituximab).

TPE can also be used prior to transplant to remove HLA antibodies. TPE (some series have used double filtration plasmapheresis and one small series used Prosorba column) is used in combination with immunosuppressive drugs pre transplant until crossmatch is negative. TPE is usually continued postoperatively also and re-initiated in cases where AMR occurs. The ability to obtain a negative crossmatch depends on the DSA titer. Using approximately 5 TPE pre-operatively, will allow the titer of ≤32 to become negative. The risk of AMR is approximately 40% with approximately 90% 1-year graft survival. The desensitization protocols should be used only in highly selected patients.

Technical notes

Patients should be started on immunosuppressive drugs prior to initiating TPE to limit antibody resynthesis. For desensitization protocols, there appears to be a correlation between the number of TPEs needed pre-operatively to obtain a negative crossmatch and the antibody titer.

Volume treated: 1 to 1.5 TPV **Replacement fluid:** albumin	**Frequency:** daily or every other day

Duration and discontinuation/number of procedures

For AMR, some protocols use a set number of procedures, usually 5 or 6, daily or every other day. Other protocols guide number of treatments based on improvement in renal function and decrease in DSA titers. It is also undecided if low dose IVIG (100 mg/kg) should be used after every procedure or at the end of the series or not at all.

For desensitization protocols, TPE is performed daily or every other day per protocol until crossmatch becomes negative. TPE is also performed post-operatively for a minimum of 3 procedures. Further treatment is determined by risk of AMR, DSA titers, or the occurrence of AMR.

References [627–640]

*As of October 30, 2009 using PubMed and the MeSH search terms antibody mediated rejection, kidney transplant, HLA desensitization and plasmapheresis and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

RHEUMATOID ARTHRITIS, REFRACTORY

Incidence: 500-1000 per 100,000/year				Procedure	Recommendation	Category
				IA	Grade 2A	II

# of reported patients*: 100-300					
RCT	**CT**	**CS**	**CR**	**Type of evidence**	
1 (99)	2 (26)	2 (95)	6 (6)	Type I	

Description of the disease

Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disease of unknown etiology. The most characteristic feature is an inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. RA hallmark is synovial inflammation leading to cartilage damage, bone erosions and subsequent changes in joint integrity. RA affects all ages and ethnic origins, most commonly women between 40-60. There is a genetic predisposition with the class II major histocompatibility allele HLA-DR4 and related alleles which is particularly strong for patients with antibodies to cyclic citrulinated peptides (anti-CCP). 20% of patients, most commonly those with high titers of rheumatoid factor (RF) or anti-CCP, have extra-articular features which might involve skin, eyes, lungs, heart, blood, and blood vessels. Overall, about 80% of patients are RF(+). More recently, anti-CCP is considered in the pathogenesis and establishing the diagnosis of RA. It is also suggested that although the original stimulus has not been characterized, the propagation of RA is immunologically mediated and cytokines such as IL-1 and TNF are involved in bone and cartilage destruction.

Current management/treatment

The goals of therapy are relief of pain, reduction of inflammation, protection of articular structures, maintenance of function, and control of systemic involvement. The current therapeutic interventions are palliative, not curative, and are aimed primarily at relieving signs and symptoms of the disease. Medical management involves five groups of medications. (1) Nonsteroidal anti-inflammatory drugs, simple analgesics and cyclooxygenase-2 selective inhibitors, have been shown to control the symptoms and signs of the synovial inflammatory process. (2) Low-dose oral glucocorticoids suppress inflammatory signs and symptoms, as well as may retard the development and progression of bone erosions. (3) Disease modifying anti-rheumatic drugs (DMARDs), including methotrexate, sulfasalazine and hydroxychloroquine, have the capacity to decrease elevated levels of acute phase reactants, and thus modify the inflammatory component and its destructive capacity. There is clinical improvement and frequently an improvement in serologic evidence of disease activity. DMARDs should be started as soon as the diagnosis is established, especially in patients with evidence of aggressive disease with a poor prognosis. Combinations of DMARDs appear to be more effective than single agents. (4) Biologics, which include TNF-neutralizing agents (infliximab, etanercept and adalimumab), IL1-neutralizing agents (anakinra), anti-CD20 (Rituximab), and those that interfere with T cell activation (CTLA4-Ig, abatacept), improve signs and symptoms and slow the progressive damage to articular structures in DMARD failures as well as in DMARD-naïve patients. (5) Immunosuppressive and cytotoxic drugs, including leflunomide, cyclosporine, azathioprine, and cyclophosphamide, are reserved for patients who have failed DMARDs and biologics.

In a sham-controlled randomized trial, immunoadsorption (IA) using the Staphylococcal protein A (SPA) silica column was shown to be more effective than ''placebo''. Analysis of 68 patients who completed all treatments and follow-up indicated 42% response in the IA-treated patients compared to 16% in the sham-treated patients. In intent-to treat analysis of all 99 patients who were randomized, the corresponding response rates were 29% and 11%. Both analyses were statistically significant. IA is a therapeutic option only for patients who have failed treatment with traditional DMARDs as well as newer biologic agents, and who have severe active refractory disease.

Few reports including one controlled trial of 82 patients have used double filtration plasmapheresis (DFPP) for active refractory RA with significant improvement.

Rationale for therapeutic apheresis

The rationale for using the SPA silica column was the observation that protein A has a high affinity for Fc portion of IgG and for high molecular weight IgG and IgM complexes, such as RF and circulating immune complexes (CICs). Thus, IgG antibodies and CICs can be selectively removed from the circulation by extracorporeal exposure of patient's plasma to SPA immobilized on a solid matrix. CICs might have an immunosuppressive role in autoimmune diseases and their removal or alteration by IA, could be immunomodulatory and potentially beneficial for RA patients. It was shown though that only relatively small amounts of immunoglobulins are removed by IA (1-3% of total serum immunoglobulins) and their concentrations are unchanged as well as plasma levels of CICs. Thus, the precise mechanism of action remains unclear and is probably multifactorial. The slow onset and sustained duration of immunoadsorption-induced therapeutic responses in RA suggest an indirect immunomodulatory mechanism. Possible indirect immunomodulation mechanisms include: the release of protein A into the circulation, which induces development of SPA inhibitory activity, presumably antibody-mediated (responsive patients have significantly higher levels of SPA antibodies than those who are not responsive); complement activation, which solubilizes previously formed immune precipitates and prevents immune precipitation; formation of larger CICs, which are cleared by the immune system as abnormal; and SPA may function as a superantigen to modify the B cell repertoire.

DFPP selectively removed high molecular-weight substances such as immunoglobulins and CIC.

Technical notes

For RA, IA using the SPA silica column can be done after separation of plasma by continuous-flow cell separator. Plasma is treated by perfusion through the column and then reinfused with the flow rate not exceeding 20 mL/min. Common adverse effects include fatigue, chills, low-grade fever, musculoskeletal pain, hypotension, nausea, vomiting and short-term flare in joint pain and swelling following treatment. Serious adverse events reported were cutaneous vasculitis or rash which necessitates temporary discontinuation of the procedures until it is resolved. There is no increase potential for malignancy or immunosuppresion. Contraindications to IA include concomitant use of angiotensin converting enzyme inhibitor, known hypercoagulable state or history of thrombotic event.

Volume treated: 1,200 mL plasma	**Frequency:** once a week for 12 weeks
Replacement fluid: not applicable	

Duration and discontinuation/number of procedures

In most studies, clinical improvement was delayed for up to few weeks after completing the procedures. In the RCT study, non-responders who were treated a second time had a 0% response rate.

References [641–654]

*As of October 1, 2009 using PubMed and the MeSH search terms rheumatoid arthritis, immunoadsoption, prosorba column, and extracorporeal protein A immunoadsorption for articles published in the English language. References of the identified articles were searched for additional cases and trials.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Incidence: 19-75 per 100,000/year; >8:1 (F:M)	Procedure	Recommendation	Category
	TPE	Grade 2C	III
	ECP	Grade 1A	IV

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
TPE	0	3 (75)	6 (60)	17 (18)	Type II-2
ECP	3 (162)	0	3 (62)	NA	Type I

Description of the disease

Systemic sclerosis (SSc), or scleroderma, is a chronic multisystem disorder of unknown etiology with worldwide distribution characterized clinically by thickening of the skin cause by accumulation of connective tissue and by involvement of visceral organs, including the gastrointestinal tract, lungs, heart, and kidneys. Abnormalities in microvasculature are typical and prominent features of SSc. SSc patients present with either with diffuse cutaneous scleroderma (i.e. symmetric skin thickening of proximal and distal extremities, face and trunk) or with limited cutaneous scleroderma (i.e., symmetric skin thickening limited to distal extremities and face). The latter group usually presents with features of CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Teleangiectasia). Raynaud's phenomenon is an initial symptom of SSc in the majority of patients. The severity of visceral disease determines survival as it affects critical organs [e.g., lungs (interstitial fibrosis), heart, liver (biliary cirrhosis), and/or kidneys (renovascular hypertensive crisis]. Antinuclear antibodies are present in more than 95% of patients with SSc. Antinuclear and anti-nucleolar antibodies are directed against topoisomerase 1 (Scl 70/40%), centromere (60–80%), RNA polymerase I, II, and III (5–40%), Th RNP (14%), U1 RNP (5–10%), and PM/Scl (25%). Accumulation of collagen and other extracellular matrix proteins including fibronectin, tenascin, and glycosaminoglycans, in skin and other organs is characteristic for SSc. A state of chronic ischemia caused by an injury to endothelial cells in small arteries, arterioles, and capillaries precedes fibrosis. The current understanding of pathophysiology implicates cell mediated immunity involving activated T cells and IL-2, increased ratio of circulating CD4 cells to CD8, and significant involvement of macrophages and their products IL-1, IL-6, TNF-α, TGF-β, PDGF, and fibronectin.

Current management/treatment

Treatment of involved organ systems can relieve symptoms and improve function, though SSc is not curable at this time. D-Penicillamine is the most widely used drug and has been shown in a retrospective study to improve the skin thickening and survival of patients, when compared to no treatment. In rapidly progressive disease, corticosteroids, azathioprine, methotrexate, cyclophosphamide, and other immunosuppressants have been used. Symptomatic treatment of Raynaud's phenomenon with calcium channel blockers may provide symptomatic relief, but can be associated with aggravation of GI symptoms. Raynaud's phenomenon complicated by digital ulcers and pulmonary hypertension may respond to intravenous prostacyclin. ACE inhibitors have dramatically improved the typically poor outcome of renal hypertensive crisis. The newer treatment modalities include the use of minocycline, psoralen-UV-A, lung transplantation, etanercept, and thalidomide. However, no medications appear to be truly effective in patients with aggressive disease. A clinical benefit was observed in total of 46 patients who underwent high dose chemotherapy followed by autologous hematopoietic progenitor cell salvage.

Rationale for therapeutic apheresis

Pathophysiology of SSc is not fully elucidated but, as presently understood, lends little support to the use of plasma exchange as a treatment option. There is no known circulating factor, pivotal in pathogenesis of this disease, which could be easily identified and removed. Nevertheless, there are several controlled trials as well as case series spanning over the last 20 years. A controlled trial of 23 patients randomized to no apheresis, plasma exchange, or lymphoplasmapheresis was reported in 1987 as an abstract. Both treatment groups showed statistically significant improvement in skin score, physical therapy assessment, and patient and physician global assessment. The study has never been published in the peer-reviewed literature. An effect of long term TPE was evaluated in a controlled trial. The TPE were scheduled as 2–3 weekly for 2 week, 1 TPE weekly for 3 months, and 1 TPE every other week as a maintenance therapy. One volume exchange was used with 4% albumin as a replacement fluid. All serological markers improved in comparison to the control group; however, there was no difference in clinical outcomes between the groups. In a case series reporting on 15 patients who received TPE in combination with prednisone and cyclophosphamide, 14 patients had clinical improvement. Severe gastrointestinal symptoms were ameliorated in 4 patients, severe polymyositis was largely reversed in 2 patients, and pulmonary and cardiac function was improved in others. Involvement of activated T lymphocytes could lead to the use of other apheresis modalities such as extracorporeal photopheresis (ECP). There were three randomized controlled trials using ECP in SSc.

Technical notes

See the introduction to this article.

Volume treated: 1 to 1.5 TPV	**Frequency:** 1 to 3 per week
Replacement fluid: albumin	

Duration and discontinuation/number of procedures

The length of treatment with TPE varies widely. A course of six procedures over the course of 2–3 weeks should constitute a sufficient therapeutic trial.

References [655–658]

*As of November 6, 2009 using PubMed and the MeSH search terms scleroderma, progressive systemic sclerosis and apheresis and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

SEPSIS WITH MULTIORGAN FAILURE

Incidence: 300 per 100,000/year in the US				Procedure	Recommendation	Category
				TPE	Grade 2B	III

# of reported patients*: >300						
RCT	CT	CS	CR	Type of evidence		
3 (146)	3 (90)	8 (149)	3	Type I		

Description of the disease

Sepsis, a systemic inflammatory response to infection, is the most common cause of death in non-coronary intensive care units and the 10th most common cause of death in the United States. It accounts for 2–3% of all hospital admissions. The incidence of sepsis has increased over the last two decades with an unchanged mortality rate of 28–50%.

Signs and symptoms consist of fever or hypothermia, tachycardia, hyperventilation, and leukocytosis or leukopenia. Organ dysfunction, hypoperfusion, and hypotension can be seen. Risk factors include age extremes, chronic medical conditions, immune compromise, indwelling catheters and devices, and disruption of natural defense barriers. Sepsis is a complex process consisting of activation of a variety of host defense systems. Production of a wide variety of inflammatory molecules can lead to organ dysfunction or an anti-inflammatory response resulting in an immunocompromised state. Cytokines and other mediators in sepsis include TNF, IL-1, IL-2, IL-6, IL-8, leukotrienes, prostaglandins, endotoxin, and TGF-β.

Current management/treatment

Management includes antimicrobial agents and control of the source of the infection, hemodynamic support including volume and vasopressors, oxygenation and ventilatory support, and avoidance of complications. Additional innovative treatments have included the administration of corticosteroids, monoclonal antibodies to TNF, soluble TNF receptor, antithrombin, activated protein C, and tissue factor pathway inhibitor. These therapies seek to interrupt the cascade of inflammation and anti-inflammatory response.

Rationale for therapeutic apheresis

Attempts to block or remove single mediators of sepsis have been somewhat successful. TPE, due to its non-selective nature, has the potential to remove multiple toxic mediators of the syndrome and may therefore be more effective than blocking single components of the process. In addition, if plasma is used as the replacement solution in TPE, substances consumed during the systemic inflammatory process, such as ADAMTS13, would be replaced which in turn could have a favorable influence on the pathophysiology of sepsis and patient outcomes.

Three case reports have been published which suggest benefit. Non-randomized clinical trials and case series of TPE have found survivals of 66 to 87% compared to either predicted or historical control survivals of 20 to 40%.

Three randomized trials of 106, 30, and 10 patients have been published. The largest randomized trial by Busund et al found 28-day mortality rates of 33% in the TPE group compared to 53.8% in the control group (p<0.05). When differences between the control and experimental groups were considered using multiple logistic regression, the significance of the treatment variable on mortality was p=0.07. In this study, patients received a single TPE with one additional TPE the next day if there was no improvement or hemodynamic instability developed. A trial by Reeves et al using continuous plasmafiltration examined 22 adults and 8 children. No difference in mortality was seen between the control group and those treated with plasmafiltration. Reduction of some acute phase reactants was seen (C3, CRP, haptoglobin, and α_1-antitrypsin). Finally, in the trial by Nguyen et al, 10 children were randomized to TPE or standard treatment. Decrease in organ severity score and improved survival was seen in the TPE group. This resulted in the trial being stopped early due to the interim analysis showing significant improvement in the treatment group.

Technical notes

Both centrifugal based and filtration based apheresis instruments have been used in the trials of TPE. There has also been suggestion by some authors that early performance of TPE may be more beneficial than waiting and may explain discrepancies in some series and trials. In the presence of severe coagulopathy, plasma alone is indicated as a replacement fluid. Because these patients are severely ill with hypotension and cardiovascular instability, treatment should be performed in an appropriate setting, such as an intensive care unit, and the patients monitored closely.

The trials, case series, and case report numbers given above refer to reports of the use of TPE in the treatment of sepsis. In addition to TPE, a number of selective removal columns have also been examined. The polymyxin B columns consist of polymyxin B bound to polystyrene fibers. Whole blood is perfused through the column which binds endotoxin. A randomized trial of 70 patients found a 54% survival in the treatment arm compared to a 36% survival in the control arm. A case series of 99 patients, survival of 66% was seen compared to an expected survival of 20%. These patients received treatments lasting two hours though the frequency and total volume treated were not given. The Matisse column contains human albumin bound to polymethacrylate. Whole blood is passed through this column which binds endotoxin. A randomized trial involving 145 patients found no difference in survival but a non-significant trend towards a shorter ICU stay. These columns used to treat 1–1.5 blood volumes daily for four days. Neither of these devices has been approved for use in the United States.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily
Replacement fluid: albumin; plasma	

Duration and discontinuation/number of procedures

The RCT of Busund et al limited treatment to one to two TPE. The RCT performed by Nguyen et al performed up to 14 TPE. Case series have treated patients daily until improvement. In many, ''improvement'' has not been defined while in other series it has been variably defined as resolution of DIC, decrease in hemodynamic support, reversal of multisystem organ dysfunction, and improvement in laboratory values.

References [659–670]

*As of October 8, 2009 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and sepsis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

SICKLE CELL DISEASE

Incidence: 289 per 100,000 African-Americans, 89.8 per 100,000 Hispanics primarily from Caribbean islands (1 in 375 for Hb SS, 1 in 835 for Hb SC, 1 in 1,667 for Hb S/β-thalassemia among African-American live births)	Procedure	Recommendation	Category
	RBC exchange	Grade 1C	I (Acute stroke)
			II (Acute chest syndrome)
	RBC exchange	Grade 1C	II (Prophylaxis for primary or secondary stroke prevention of
	RBC exchange	Grade 1C	transfusional iron load)
	RBC exchange	Grade 2C	III (Multiorgan failure)

# of reported patients*: >300	RCT	CT	CS	CR	Type of evidence
Acute stroke	0	0	7 (160)	7 (9)	Type II-3
Acute chest syndrome	0	0	12 (142)	8 (8)	Type II-3
Prophylaxis for primary or secondary stroke prevention of transfusional iron load	0	0	18 (310)	3 (3)	Type II-3
Multiorgan failure	0	0	3 (10)	2 (2)	Type II-3

Description of the disease

Sickle cell disease (SCD), the most common inherited blood disorder in the US, is caused by an abnormal hemoglobin (Hb) due to substitution of valine for glutamic acid at β6 (HbS). The most common type is sickle cell anemia, in which the individual is homozygous for the βˢ gene (Hb SS). Variants of SCD include Hb SC, Hb β-thalassemia, Hb SD, etc. Morbidity and mortality are significantly higher in HbSS than in SCD variants. Diagnosis is made by isoelectric focusing and cellulose acetate electrophoresis. RBCs containing HbS have a shortened lifespan, resulting in chronic hemolytic anemia. HbS polymerizes upon deoxygenation, causing RBCs to become rigid and deformed (sickled RBCs) occluding the microvasculature leading to tissue hypoxia and infarction. Major manifestations are vaso-occlusive events (VOEs), splenic sequestration, and transient red cell aplasia (RCA). Painful episodes are the most common VOE. Other serious VOEs include acute chest syndrome (ACS), stroke, priapism, and splenic, hepatic, and renal dysfunction. Leading causes of death are sepsis, ACS, stroke, and acute multiorgan failure. While infection is the most common cause of death in children, pulmonary hypertension is the most common cause of death in adults. Overall mortality rate for SCD is 2.6% (0.5 deaths/100 person years) with the peak at 1 to 3 years of age. Average life expectancy was in the 40's in the mid 1990s.

Current management/treatment

Standard therapies include folic acid to support increased erythropoiesis, pneumococcal and Haemophilus influenzae vaccinations and penicillin for infection prophylaxis, analgesics for painful episodes, and antibiotics for infections. Hydroxyurea (HU) has been efficacious in reducing frequency of painful episodes and ACS and other severe VOEs. RBC transfusion (Tx) in the form of simple transfusion (S-Tx) or exchange transfusion (Ex-Tx) is the first-line adjunct therapy in acute and chronic complications. Ex-Tx can be either manual or automated (RBC exchange). Acute S-Tx is indicated for symptomatic anemia due to increased hemolysis, RCA, splenic sequestration, ACS with hypoxia, stroke, acute multiorgan failure, before surgery or in complicated pregnancy. RBC exchange is increasingly used in the treatment of severe acute complications and has been shown to be effective in selected cases. Chronic Tx to maintain HbS <30% is indicated for prevention of primary and secondary stroke and HbS <30-50% to treat chronic debilitating pain, pulmonary hypertension, and anemia with chronic renal failure. Manual Ex-Tx is labor intensive, prolonged and less efficient than RBC exchange. Both types of Ex-Tx used as initial or chronic Tx therapy for patients with stroke are more effective in preventing subsequent stroke than S-Tx, but outcome is not better than S-Tx in reducing perioperative complications and for management of adult patients with ACS. However, RBC exchange appears to be effective in improving respiratory distress in children with ACS. Prophylactic RBC exchange during pregnancy is associated with a lower risk of intrauterine growth restriction. As alternatives to HU or chronic Tx, hematopoietic stem cell transplantation from an HLA-identical sibling, partially matched family members or unrelated or related umbilical cord blood unit is an option for patients with first/primary stroke.

Rationale for therapeutic apheresis

In severe anemia, S-Tx is the best Tx method to improve oxygen-carrying capacity of blood by increasing RBC mass. In acute ischemic stroke, ACS, acute hepatic crisis, or acute life- or organ-threatening complications, RBC exchange is preferred as the HbS concentration is reduced rapidly by replacing RBCs containing HbS with normal RBCs without causing hyperviscosity or volume overload. However, advantages of RBC exchange over S-Tx through randomized controlled clinical trials have not been documented. Long-term RBC exchange has the distinctive advantage of preventing or markedly reducing transfusional iron accumulation, but is associated with significantly higher (1.5 to 3 times higher) blood requirements than S-Tx. Increased blood donor exposure can potentially increase rates of viral transmission and RBC alloimmunization. Strategies to reduce the risk of alloimmunization include the use of racially- and partial phenotypically-matched RBC.

Technical notes

Apheresis equipment calculates the replacement packed-RBC volume to achieve the desired target HbS (FCR) and hematocrit levels. Guidelines to calculate replacement volume using COBE Spectra are: 1) END Hct at 30 ± 3% (≤36% to avoid hyperviscosity) and 2) FCR (desired fraction of patient's RBCs remaining at end of procedure) at 25 to 30%. In recently transfused patients, calculate the FCR by dividing the desired Hb S level by pre-apheresis HbS level multiplied by 100. To maintain isovolemia, primed saline is not diverted and RINSEBACK is omitted at the end of the run. In children, clinically unstable or severely anemic patients, RBC priming is required. Modification of RBC exchange utilizing isovolemic hemodilution, which consists of RBC depletion with 0.9% NaCl replacement followed by standard RBC exchange, reduces replacement packed-RBC volume.

Volume treated: volume necessary to achieve: a FCR <40% (one RBC volume) or <30% (1.5-2 × RBC volumes).

Replacement cells: HbS negative leukoreduced RBCs and, if available, antigen-matched for at least E, C, and Kell.

Frequency: Acute, one procedure to achieve the target HbS level <30%; Chronic, every 3-4 weeks to maintain the target HbS level <30%, every 4-5 weeks to maintain the target HbS level <50%

Duration and discontinuation/number of procedures

Duration and number of RBC exchanges depend upon clinical indications, for example, one RBC exchange for treatment of acute, severe, or organ-threatening complications, short-term transfusion for chronic debilitating pain, and life-long transfusion for stroke prevention, etc.

References [671–688]

*As of December 31, 2009 using PubMed and the MeSH search terms sickle cell disease, red blood cell exchange transfusion, and erythrocytapheresis for articles published in the English language. References of identified articles were searched for additional cases and trials.

SYSTEMIC LUPUS ERYTHEMATOSUS

Incidence: 15-50 per 100,000/year	Procedure	Recommendation	Category
	TPE	Grade 2C	II (severe)
	TPE	Grade 1B	IV (nephritis)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
TPE	1 (20)	1 (4)	14 (128)	61 (63)	Type I
TPE (nephritis)	2 (36)	2 (114)	6 (160)	10 (11)	Type I

Description of the disease

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder where circulating autoantibodies, immune complexes, and complement deposition leads to cell and tissue injury. The disease preferentially affects childbearing age females (ratio F:M 10:1). Ethnicity may affect disease severity, with African Americans presenting with more severe forms. Mortality of 70% at 10 years is typically due to infections and renal failure. Clinical symptoms may be non-specific (e.g. fatigue, malaise, fever, anorexia, nausea, weight loss) and/or directly attributable to the involvement of one or more organ systems. The disease can affect any organ. Renal involvement in SLE (i.e. lupus nephritis) is associated with high mortality, but the extent and rate of progression is highly variable. Pathogenesis of SLE seems to be more complex than simple deposition of DNA-antiDNA complexes. Recent observations point towards nucleosomes and possibly complement factor C1q as major factors in SLE pathogenesis. The nucleosome serves as an autoantigen in SLE and is presented to pathogenic T helper and B cells. A defect in apoptosis is also postulated to be an important factor in autoimmunity. Laboratory testing is helpful in establishing diagnosis. Screening tests for antinuclear antibodies (ANA) are commonly positive while the more specific antibodies to double-stranded DNA (anti-dsDNA) and Sm antibodies are used as confirmatory tests. Low complement levels and high titers of autoantibodies suggest active disease. Recent studies also underscore potential role of T regulatory cells [CD4+CD25(high)FoxP3+], which are significantly decreased in the patients with SLE.

Current management/treatment

SLE is an incurable chronic, remitting, and relapsing illness. Therapy entails immunosuppressive agents such as cyclophosphamide, azathioprine, prednisone, methotrexate, cyclosporine and mycophenolate mofetil. Newer agents directly target abnormal immune cells and include rituximab (anti-CD20), epratuzumab (anti-CD22) and the anti-dsDNA tolerogen LJP394. Other promising approaches include inhibition of the CD40-CD40 ligand pathway (anti-CD40 ligand monoclonal antibody), inhibition of the B7 pathway (CTLA-4 antibody), the blockade of IL-10, and anti-tumor necrosis factor therapy but controlled trials of these agents have not been performed. Patients with end-stage nephritis are treated with dialysis and renal transplantation. In addition, there are ongoing Phase I/II trials using autologous HSCT with high dose chemotherapy in SLE.

The SLE Disease Activity Index (SLEDAI) and the SLE Activity Measure (SLAM) are used to determine disease activity. The SLEDAI consists of 19 items representing nine organ systems. Each item is rated as present or absent. The SLEDAI score above 5.0 defines active disease. The SLAM includes 24 clinical manifestations for nine organ systems and eight laboratory variables to evaluate organs that cannot otherwise be assessed. All items are scored as 0 to 2 or 0 to 3 according to their severity. Evaluation of therapy efficacy in SLE typically includes one or both scores. The relationship between clinical impression and SLEDAI score has been recently evaluated with the following proposed: flare (an increase in SLEDAI by >3), improvement (a reduction of SLEDAI by >3), persistently active disease (a change in SLEDAI ± ≤3) and remission (SLEDAI of 0).

Rationale for therapeutic apheresis

TPE was initially used to treat SLE under the assumption that reduction in autoantibody concentration would change the rate of disease progression. This rationale has not translated into a clear clinical response. In the early 1980's it was reported that more than 50% of patients with various manifestations of SLE improved after TPE. However, the first RCT in mild SLE, where the patients underwent six four liter exchanges within two weeks with expected autoantibody and immune complex reductions, showed no clinical improvement. More recently, the use of cyclosporine A and TPE to control symptomatic disease in a prospective trial of 28 patients with flares resulted in quicker resolution of symptoms and decreased doses of cytotoxic drugs. Multiple well documented case reports of beneficial effect of TPE in SLE associated TTP, pulmonary hemorrhage, MG, hyperviscosity and cryoglobulinemia have been published. A recent review of 26 patients with SLE and CNS involvement who were treated with TPE or combination TPE/cyclophosphamide revealed that 74% of patients improved, 13% stabilized, and 13% progressed. These results highlighted a potential benefit for refractory or critically ill patients. Addition of TPE to immunosuppressive therapy in SLE patients with diffuse alveolar hemorrhage has been also reported.

In a small non-controlled trial of patients (n=5) undergoing TPE in the setting of severe SLE, it has been reported that during the course of TPE (4-6 days) the peripheral level of CD4+CD25(high)FoxP3+ cells significantly increased. The increased number of T regs was accompanied by a decrease in the disease activity as measured by SLEDAI. This observation could be due to the elimination of interpheron alpha and lymphocytotoxic antibodies.

TPE in lupus nephritis is classified as Category IV as a controlled trial of TPE plus prednisone and cyclophosphamide versus prednisone and cyclophosphamide in patients with severe lupus nephritis showed no benefit. Smaller later trials have supported these findings.

Technical notes

See the introduction to this article.

Volume treated: 1 to 1.5 TPV	**Frequency:** Lupus cerebritis or SLE with DAH: daily to every other day; SLE other: one to 3 times a week
Replacement fluid: albumin; plasma	

Duration and discontinuation/number of procedures

Typically a course of 3 to 6 TPE is sufficient to see response in the patients with lupus cerebritis or DAH. Prolonged treatments have been reported but its efficacy and rationale is questionable.

References [101,689–703]

*As of January 30, 2010 using PubMed and the MeSH search terms systemic lupus erythematosus, plasmapheresis, apheresis, and photopheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

THROMBOCYTOSIS

Incidence: 0.59-2.53 per 100,000/year essential thrombocythemia (ET); 0.02-2.8 per 100,000/year polycythemia vera (PV) Prevalence: 22-24 per 100,000 for ET and PV	Procedure	Recommendation	Category
	Thrombocytapheresis	Grade 2C	II (symptomatic thrombocytosis)
	Thrombocytapheresis	Grade 2C	III (prophylaxis or secondary thrombocytosis)

# of reported patients*: 100-300

	RCT	CT	CS	CR	Strength of evidence
Myeloproliferative neoplasms	0	0	7 (180)	22 (27)	Type II-3
Secondary thrombocytosis	0	0	2 (39)	3 (4)	Type II-3

Description of the disease

Thrombocytosis, defined as a circulating platelet count $\geq$450-500 $\times$ 10^9/L, is most commonly a secondary reaction to acute bleeding, hemolysis, infection, inflammation, asplenia, cancer or iron deficiency. The increased normal platelets in these cases do not predispose to thrombosis or bleeding. By comparison, the functionally abnormal platelets with myeloproliferative neoplasms (MPNs) are causally linked to vascular complications. Polycythemia vera (PV) and essential thrombocythemia (ET) are clonal MPNs characterized by autonomous overproduction of predominantly red cells and platelets, respectively. A *JAK2* gene point mutation is found in roughly >95% and 60% of PV and ET cases, respectively. Arterial or venous thromboembolic events with PV or ET occur either spontaneously or during situational hypercoagulability, such as surgery and pregnancy. Clinical risk factors also include age >60 years and history of prior thrombosis. Uncontrolled erythrocytosis (hematocrit >55%) contributes to risk with PV while cardiovascular comorbidities and leukocytosis at diagnosis have been implicated with ET. The cumulative rates of thromboembolism with PV and ET range from 2.5-5% and 1.9-3% per patient per year, respectively; recurrent thrombosis occurs at 5.6-7.6% patient-years. Anticoagulation or anti-platelet agents and cytoreductive therapy significantly lower the risk of recurrent thromboembolism. Microvascular ischemia of the digits or central nervous system can also occur with ET and PV. Thrombosis risk with MPNs is not directly related to the circulating platelet number. Bleeding, which usually occurs in mucocutaneous sites, affects 4-37% and 2-20% of individuals at diagnosis with ET or PV and develops during the disease in 1-7% and 2% of cases, respectively. Hemorrhagic risk is greatest with platelet counts >1,500 $\times$ 10^9/L, related to development of acquired von Willebrand syndrome (AVWS). Splenectomy, performed for palliation of pain or cytopenias in late stage PV, ET or chronic primary myelofibrosis (PMF), is associated with extreme ''rebound'' thrombocytosis (i.e. >1000 $\times$ 10^9/L) in 5% of cases and post-operative thrombosis (10%) and bleeding (14%); however, the platelet count does not predict thrombohemorrhagic complications.

Current management/treatment

Low-dose aspirin is indicated for thromboprophylaxis in patients with ET or PV who do not have a bleeding tendency. Phlebotomy is used with PV to maintain a normal hematocrit. Platelet-normalizing therapy, preferably with hydroxyurea, is indicated for patients older than 60 years, those with thrombosis history, younger patients with significant cardiovascular co-morbidities and those with bleeding and a platelet count >1,500 $\times$ 10^9/L. The platelet count should be normalized before surgery, particularly splenectomy, to minimize complications and avoid ''rebound'' thrombocytosis. Alternative platelet-lowering agents include anagrelide and interferon alpha (the treatment of choice during pregnancy). Venous thromboembolic complications are treated acutely with unfractionated or low-molecular-weight heparin followed by therapeutic warfarin for at least 3 to 6 months. Arterial events are treated acutely with an anti-platelet agent or, less commonly, heparin. Cytoreductive therapy with hydroxyurea is most important for preventing recurrent thromboembolism. Secondary prevention also includes warfarin or an anti-platelet agent. Thrombocytapheresis is only considered for exceptional circumstances.

Rationale for therapeutic apheresis

Thrombocytapheresis (therapeutic plateletapheresis) has been utilized anecdotally to prevent recurrent or progressive thromboembolism or hemorrhage in selected patients with a MPN, uncontrolled thrombocytosis and a serious, acute event. Case reports describe rapid improvement of severe microvascular ischemic complications that are unresponsive to anti-platelet agents. Thrombocytapheresis has also been used to treat extreme ''rebound'' thrombocytosis after splenectomy and during pregnancy to prevent recurrent fetal loss in high-risk patients; although it is not indicated or beneficial for standard-risk pregnant women with PV or ET. Although the therapeutic mechanisms are not well defined, rapid cytoreduction is believed to ameliorate prothrombotic factors associated with the dysfunctional platelets. Restorating a normal platelet count corrects the short plasma half-life of large von Willebrand factor multimers with ET; and this may be important for patients with AVWS and >1,500 $\times$ 10^9/L platelets. Platelet-lowering agents must be given to prevent rapid reaccumulation of circulating platelets. Thrombocytapheresis may be considered for selected high-risk patients when cytoreductive agents are contraindicated or intolerable or when pharmacologic therapy would be too slow (e.g. before urgent surgery). Although anecdotal case reports have described a possible benefit of thrombocytapheresis with secondary thrombocytosis, the rationale is undefined and efficacy unproven.

Technical notes

Each procedure lowers the platelet count by 30 to 60%. A central venous catheter may be required for multiple treatments or long-term therapy. Anticoagulant ratio of whole blood: anticoagulant should be 1:8-12, and heparin should be avoided to prevent ex vivo platelet clumping. Methods of thrombocytapheresis typically differ from donor platelapheresis, thus manufacturer's recommendations as well as published reports should be carefully considered prior to initiation of the procedure.

Volume treated: 1.5 to 2 TBV **Replacement fluid:** none; crystalloid	**Frequency:** daily; or as indicated for chronic management

Duration and discontinuation/number of procedures

With acute thromboembolism or hemorrhage, the goal is normalization of the platelet count and maintenance of a normal count until cytoreductive therapy takes effect. The goal for prophylaxis of high-risk patients who are pregnant, undergoing surgery or postsplenectomy should be determined on a case-by-case basis (e.g. considering the patient's history of thrombosis or bleeding at a specific platelet count). Without an informative clinical history, a platelet count of 600 $\times$ 10^9/L or less may be sufficient.

References [334,704–719]

*As of October 15, 2009 using PubMed and the MeSH search terms thrombocytosis, essential thrombocythemia, polycythemia vera, plateletapheresis, thrombocytapheresis, apheresis, myeloproliferative disorder, myeloproliferative neoplasm for reports published in the English language. References of the identified articles were searched for additional cases and trials.

THROMBOTIC MICROANGIOPATHY: DRUG-ASSOCIATED

Incidence:	Procedure	Recommendation	Category
Ticlopidine/Clopidogrel: 50 in 100,000 users	TPE	Grade 2B	I (ticlopidine; clopidogrel)
Cyclosporine/Tacrolimus: rare	TPE	Grade 2C	III (cyclosporine; tacrolimus)
Gemcitabine: 15 in 100,000 (0.015%) users	TPE	Grade 2C	IV (gemcitabine)
Quinine: rare	TPE	Grade 2B	IV (quinine)

# of reported patients*: >300

	RCT	CT	CS	CR	Strength of evidence
Ticlopidine/ Clopidogrel	0	0	4 (152)	5 (5)	Type II-3
Cyclosporine/ Tacrolimus**	0	0	6 (90)	7 (7)	Type II-3
Gemcitabine	0	0	2 (10)	9 (11)	Type II-3
Quinine	0	0	3 (32)	8 (8)	Type II-3

**Evaluated in aggregate since these are frequently prescribed on alternating or tandem schedules.

Description of the disease

Thrombotic microangiography (TMA) refers to the histopathologic findings of arteriolar microthrombi with associated intimal swelling and fibrinoid necrosis of the vessel wall. A variety of drugs have been associated with platelet activation and intravascular microthrombi either confirmed by biopsy or correlated with the clinical findings of microangiopathic hemolytic anemia (MAHA) with schistocytes and thrombocytopenia. The presence of renal dysfunction, mental status changes and fever are variable depending on the associated drug.

In quinine-associated TMA, quinine-dependent antibodies directed at platelet glycoproteins as well as granulocytes, lymphocytes and endothelial cells have been documented. In cyclosporine/tacrolimus associated TMA reported patients frequently do not have systemic manifestations of TMA. Severe deficiency (<10%) of ADAMTS13 and inhibitors to its activity have been documented in ticlopidine associated TMA and less typically in clopidogrel-TMA suggesting there may be distinct mechanisms for TMA for these two related thienopyridine drugs.

Current management/treatment

Initial management of drug-associated TMA characteristically involves discontinuation of the suspected drug or in some situations, reduction of dose when discontinuation is not a medical option. Supportive care and other specific interventions in addition to TPE reported for specific drugs include: Gemcitabine- dialysis, anti-hypertensives, corticosteroids; Cyclosporine/ Tacrolimus- change to different immunosuppressive drug; and Quinine- corticosteroids, anti-platelet agents.

Rationale for therapeutic apheresis

No randomized clinical trials have addressed the efficacy of TPE for drug-associated TMA. The use of TPE for TMA is based on extrapolation of its effectiveness for idiopathic TTP. When measured, plasma ADAMTS13 protease levels have not demonstrated severe ADAMTS13 deficiency or inhibitors for many pharmaceuticals associated with TMA, thienopyridines being the primary exception. Not all patients with drug-associated TMA have hematologic manifestations. Alternative mechanisms proposed include autoimmunity, drug-dependent antibodies, and endothelial toxicity. Therefore, a therapeutic rationale for TPE is difficult to define, a fact that likely reflects the reported heterogeneous clinical results. In addition to pathogenic distinctions from primary idiopathic TTP, there may be confounding variables including the presence and progression of pre-existing medical conditions such as malignancy, renal failure, or hypertension. When patients present with MAHA and thrombocytopenia with other clinical and laboratory data consistent with TTP, TPE has been variably applied for management of drug-associated TMA. However, the mechanism of potential benefit is unknown and could include removal of plasma protein bound drug or metabolites. When TPE is considered for drug-associated TMA, potential benefits should be evaluated in conjunction with known risks of therapeutic apheresis, receipt of blood products, and vascular access. Specific drug information:

Ticlopidine/Clopirogrel: Patients presenting 2 or more weeks after initial exposure had improved survival (84% vs. 38%, p<0.05) with TPE.; when presenting <2 weeks after drug initiated, survival with TPE or without TPE was similar (77% vs. 78%). The presence of severely deficient ADAMTS13 activity (<10%) with autoantibodies, which is similar to idiopathic TTP, may relate to the overall response of these patients with TPE.

Cyclosporine/Tacrolimus: Response to TPE has been unpredictable even with extended duration of TPE. In one case report with documented inhibitor to ADAMTS13 and depressed activity (17%) TPE was associated with improvement.

Gemcitabine: In one case series, improvement was seen in 3/5 (60%) treated with TPE versus 2/6 (30%) who did not undergo apheresis. In another case series, 20% improved with TPE compared to 50% who did not receive TPE.

Quinine: May present clinically with MAHA and thrombocytopenia; however, the role of TPE is questionable since antibodies are not directed against ADAMTS-13. In one controlled case series comparing quinine-TMA to non-quinine TTP in TPE treated patients, mortality was 21% vs. 41%, respectively, and development of chronic renal failure was 57% vs. 16%. In uncontrolled case-series, mortality was 0% with TPE treated patients not lost to follow-up.

Technical notes

The specific TPE replacement fluid strategy and frequency are not described in the majority of published case reports. The pattern of response of platelet count, hematologic and laboratory parameters, and clinical signs may be variable and incomplete compared to patients undergoing TPE for idiopathic TTP. Otherwise, similar procedural considerations apply as with TPE for TTP.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily or every other day
Replacement fluid: plasma; plasma cryoprecipitate removed	

Duration and discontinuation/number of procedures

TPE for drug-associated TMA is usually performed daily until recovery of hematologic parameters and then either discontinued or tapered off, similar to treatment for idiopathic TTP. The therapeutic endpoint may be difficult to determine or attain because of confounding morbidity from underlying disease or other factors not yet recognized. The durability of response and frequency of relapse are undefined. Re-exposure to the associated drug should be avoided.

References: Ticlopidine/Clopidogrel [720–729]; Cyclosporine/Tacrolimus [730–742]; Gemcitabine [302,303,743–759]; Quinine [760–771]

*As of October 15, 2009 using PubMed and the MeSH search terms thrombotic microangiopathy or hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) AND plasmapheresis or plasma exchange AND the respective drug: gemcitabine, quinine, cyclosporine, tacrolimus, ticlopidine, clopidogrel, thienopyridine for reports published in the English language. References of the identified articles were searched for additional cases and trials.

THROMBOTIC MICROANGIOPATHY: HEMATOPOIETIC STEM CELL TRANSPLANT-ASSOCIATED

Incidence: HPC TA-TMA 3%-15% (recent studies)		Procedure TPE	Recommendation Grade 1B		Category III
# of reported patients*: >300					
	RCT	CT	CS	CR	Strength of evidence
HSCT-associated TMA [TA-TMA]	0	0	22 (322)	6 (6)	Type II-3

Description of the disease

Thrombotic microangiography (TMA) refers to the histopathological appearance of arteriolar microthrombi with associated intimal swelling and fibrinoid necrosis of the vessel wall. A variety of conditions and drugs can activate platelets causing their intravascular deposition as microthrombi, resulting in the clinicopathologic hallmarks of TMA: microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. TMA following allogeneic hematopoietic stem cell transplantation (also called transplant associated [TA]-TMA) appears to be primarily triggered by mechanisms of endothelial cell injury, including high-dose conditioning chemotherapy, irradiation, graft-versus-host disease (GVHD), mTOR (mammalian target of rapamycin) and calcineurin inhibitor drugs (used to prevent and treat GVHD) and infections. Damaged and apoptotic endothelial cells generate microparticles, release of von Willebrand factor (vWF) and induce platelet adhesion/aggregation and a procoagulant state. In contrast to idiopathic thrombotic thrombocytopenic purpura (TTP), the plasma ADAMTS13 protease level is not severely deficient nor is ADAMTS13 inhibitor activity detectable. The incidence of TA-TMA varies based on the diagnostic criteria and transplant-associated risk factors. Incidence rates in older studies ranged from 0.5-63.6%; however, the rates in more recent studies range from 3-15%. Risk factors associated with TA-TMA include higher dose conditioning regimens, acute GVHD, female sex, active infections, unrelated donor transplants and the combination of mTOR and calcineurin inhibitor drugs. Controversy exists whether non-myeloablative conditioning regimens are associated with greater risk. Kidneys are the major target organs of TA-TMA. Renal function test elevation is common and renal failure is a poor prognostic feature. Diagnostic criteria require MAHA (with high LDH or low haptoglobin) with or without unexplained thrombocytopenia, renal and/or neurologic dysfunction. Because MAHA can be due to other causes and drugs, the published criteria for TA-TMA diagnosis are relatively insensitive. TA-TMA carries a poor prognosis. Mortality rates range from 44-90%, including those patients who respond to interventions, due to renal failure, cardiac or brain ischemia, bleeding and complications of concurrent GVHD and/or infections.

Current management/treatment

Initial management of TA-TMA involves reduction or discontinuation of mTOR and calcineurin inhibitor drugs (especially if used in combination) along with aggressive treatment of underlying GVHD and infections. No randomized clinical trials have addressed the efficacy of TPE for TA-TMA. Case series have reported overall response rates with TPE (usually after drug withdrawal) ranging from 0-72%, but with frequent partial responses, relapses and up to 15% procedural adverse events. One recent study of 63 patients observed TPE responses only among those who also responded to treatment of GVHD and/or infections, suggesting that plasma exchange alone does not reverse the TMA pathophysiology. A systematic review by George et al. of published cases up to 2004 noted an 82% mortality rate among 176 patients with TA-TMA who underwent TPE compared to 50% mortality among 101 patients not treated with TPE. Similarly high cumulative mortality rates were cited by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Toxicity Committee in a 2005 consensus statement that recommended plasma exchange not be considered as a standard of care for TA-TMA. Because some patients appear to respond to TPE, a trial of plasma exchange with a defined end-point could be considered as salvage therapy for selected patients with persistent/progressive TA-TMA despite resolution of infections and GVHD. Other salvage treatment options, based on anecdotal reports, might include daclizumab, defibrotide and rituximab.

Rationale for therapeutic apheresis

The use of TPE for TA-TMA is based on extrapolation of its effectiveness for idiopathic TTP. However, numerous studies have confirmed that plasma ADAMTS13 protease levels are not severely deficient nor are ADAMTS13 inhibitors detectable in patients with TA-TMA. Therefore, a therapeutic rationale is undefined and consistent with the uncertain clinical efficacy.

Technical notes

TPE for patients with TA-TMA is often complicated by thrombocytopenia, anemia and the co-morbidities related to GVHD and infections, including bleeding and hypotension. Therefore, the pattern of platelet and LDH responses may be variable and incomplete compared to patients undergoing TPE for idiopathic TTP. Otherwise, similar procedural considerations apply as with TPE for TTP.

Volume treated: 1 to 1.5 TPV	Frequency: daily; or as indicated for chronic management
Replacement fluid: plasma; plasma cryoprecipitate removed	

Duration and discontinuation/number of procedures

TPE for TA-TMA is usually performed daily until a response and then either discontinued or tapered off, similar to treatment for idiopathic TTP. The therapeutic endpoint may be difficult to determine because the platelet count and LDH levels could be affected by incomplete engraftment and post-transplant complications. Because MAHA may be caused by other disorders and drugs posttransplant, isolated persistence of schistocytes on the peripheral blood smear, without other clinical manifestations of TMA, may not preclude discontinuation of treatment.

References [304,772–785]

*As of October 15, 2009 using PubMed and the MeSH search terms thrombotic microangiopathy, stem cell transplantation, transplantation-associated TMA, transplant-associated microangiopathy for reports published in the English language. References of the identified articles were searched for additional cases and trials.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Incidence: 0.37 per 100,000/year in the US				Procedure	Recommendation	Category
				TPE	Grade 1A	I

# of reported patients*: >300					
RCT	**CT**	**CS**	**CR**	**Type of evidence**	
7 (301)	2 (133)	17 (915)	28 (48)	Type I	

Description of the disease

Thrombotic Thrombocytopenic Purpura (TTP) is a systemic thrombotic illness affecting mostly small vessels. When initially described, TTP was defined by a pentad of clinical findings: thrombocytopenia, microangiopathic hemolytic anemia (MAHA; fragmented red cells on blood smear and elevated lactate dehydrogenase), mental status changes, renal failure and fever. In current practice, however, the clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Treatment should not be initiated until other causes of systemic thrombotic microangiopathy (TMA) such as disseminated intravascular coagulopathy severe malignant hypertension, hemolytic uremic syndrome (HUS) and post-transplant TMA are ruled out. Recently TTP has been shown to be associated with a severe (<5%) deficiency of plasma ADAMTS13 (*A*disintegrin *a*nd *m*etalloproteinase with a *t*hrombospondin type 1 motif, member 13) enzyme activity, which is responsible for maintaining normal distribution of vWF multimers by cleaving ultralarge multimers released from the endothelium. The severe deficiency of ADAMTS13 is documented in 100% of patients with idiopathic TTP in 7 out of 12 studies and in 37% to 83% of patients in the remaining 5 studies. An autoantibody is identified in the majority of patients with idiopathic acquired TTP. In a recent study, IgG4 was found to be most common anti-ADAMTS13 subclass and was suggested to be related to recurrence of the disease. Congenital TTP is associated with somatic mutations resulting in severely deficient ADAMTS13 function. Severe ADAMTS13 deficiency appears to be an important proximal step in the pathophysiology of TTP. However, as noted above, some patients with idiopathic TTP have no defect in ADAMTS13 function. The role of laboratory assays that measure protease activity and anti-ADAMTS13 antibody level in medical decision-making in TTP is still evolving. At this time TTP remains a clinical diagnosis. Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP. Work to differentiate TTP from HUS (characterized by TMA, thrombocytopenia, and renal failure) is currently underway. Better understanding of which individuals suffer from HUS or TTP may result in improved treatment by identification of patients who would benefit from emergent TPE. Pregnancy, connective tissue disease, medications, infection, cancer, and transplantation are all associated with TTP, HUS TMA syndromes (see HUS, TMA Drugs and TMA HSCT-associated Fact Sheets).

Current management/treatment

TPE has decreased the overall mortality of idiopathic TTP from uniformly fatal to <10%. TPE should be initiated emergently once TTP is recognized. If TPE is not immediately available, plasma infusions may be given until TPE can be initiated. Both fresh frozen plasma (FFP) and plasma cryoprecipitate reduced (PCR) have been used as replacement fluid for TPE, with similar results in patient outcome. Corticosteroids are often used as an adjunct at 1 mg/kg/day; however, no definitive trials to prove their efficacy have been performed. Rituximab is now often used to treat refractory or relapsing TTP. Since rituximab immediately binds to CD20-bearing lymphocytes, an interval of 18-24 hours between its infusion and TPE has been practiced. Other adjuncts include vincristine and splenectomy. Although platelet counts can be very low, patients with TTP have thrombotic rather than hemorrhagic tendency. Bleeding, if present, is typically limited to skin and mucous membranes. Platelets should not be transfused unless clinically indicated. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10 to 15 mL/kg) or cryoprecipitate (which contains ADAMTS 13) or plasma derived von Willebrand factor concentrates (used to treat von Willebrand disease) have been used.

Rationale for therapeutic apheresis

TPE with plasma replacement has significantly improved patients' clinical outcomes. No other intervention has had as significant impact on the treatment of TTP. One hypothesis is that TPE removes the anti-ADAMTS13 autoantibody, while restoring ADAMTS 13 protease activity. Clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor and/or levels.

Technical notes

Transfusion of RBC, when medically necessary, may be given emergently during TPE. Clinical response with clearing of mental status usually precedes recovery of platelet count and normalization of LDH. The median number of TPE procedures to establish hematologic recovery is 7 to 8 days. The pattern of platelet response is variable and platelet count may fluctuate during treatment. Allergic reactions and citrate reactions are more frequent due to the large volumes of plasma required. Since plasma has citrate as an anticoagulant, ACD-A can be used in a higher ratio to minimize citrate reactions, especially with moderate to severe thrombocytopenia. Fibrinogen levels may decrease following serial TPE procedures with PCR as replacement. In patients with severe allergic reactions to plasma proteins or limited supply of ABO compatible plasma, 5% albumin may be substituted for the initial portion (up to 50%) of replacement. Albumin alone however has never shown efficacy.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily
Replacement fluid: plasma; plasma cryoprecipitate removed	

Duration and discontinuation/number of procedures:

TPE is generally performed daily until the platelet count is above 150×10^9/L, and LDH is near normal for 2 to 3 consecutive days. LDH is removed during TPE, therefore, may not reflect response to TPE. The role of tapering TPE over longer duration has not been studied prospectively. Persistence of schistocytes alone on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment.

References [786–795]

*As of November 8, 2009 using PubMed and the MeSH search terms thrombotic thrombocytopenic purpura, plasma exchange, plasmapheresis and rituximab reports published in the English language. References of the identified articles were searched for additional cases and trials.

THYROID STORM

Incidence: rare				Procedure	Recommendation	Category
				TPE	Grade 2C	III

# of reported patients*: <100

RCT	CT	CS	CR	Type of evidence
0	0	3 (20)	15 (19)	Type II-3

Description of the disease

Thyroid storm or accelerated hyperthyroidism is an extreme manifestation of thyrotoxicosis. This uncommon but serious complication occurs mostly in Graves' disease and less often in the setting of toxic multinodular goiter. Symptoms are usually precipitated by common conditions such as infection, trauma, surgical emergencies, or operations and, less commonly, by radiation thyroiditis, diabetic ketoacidosis, toxemia of pregnancy, or parturition. It is postulated that cytokine release and immunologic responses caused by these conditions trigger thyroid storm. Amiodarone-induced thyroid storm is more prevalent in iodine-deficient geographic areas. The crises are usually sudden in patients with preexisting hyperthyroidism that had been only partially or not treated at all. Burch and Wartofsky created a scoring system to help standardize the diagnosis of thyroid storm using the following parameters: body temperature, central nervous system involvement, gastrointestinal-hepatic dysfunction, heart rate, and presence or absence of congestive heart failure and/or atrial fibrillation. The severity of the symptoms correlates with the number of points, for a possible total of 140. A score of 25-44 is considered high risk for an imminent storm, and a score $\geq$45 is diagnostic of thyroid storm. Overall, the clinical picture is one of severe hypermetabolism. Fever is almost invariably present and may be >104 F (40 °C) with profuse sweating. Marked tachycardia and arrhythmias may be accompanied by pulmonary edema or congestive heart failure. Tremulousness and restlessness are present; delirium or frank psychosis may supervene. Nausea, vomiting, and abdominal pain may occur early in the course. As the disorder progresses, apathy, stupor, and coma follow, and hypotension can develop. If unrecognized, the condition may be fatal. This clinical picture in a patient with a history of preexisting thyrotoxicosis or with goiter or exophthalmos, or both, is sufficient to establish the diagnosis, and emergency treatment should not await laboratory confirmation. The serum thyroid hormone levels in thyroid storm are not necessarily higher than during severe uncomplicated thyrotoxicosis. However, the patient can no longer adapt to the metabolic stress. Thus, there is no arbitrary serum T_3 or T_4 concentration that discriminates between severe thyrotoxicosis and thyroid storm. It is prudent to consider the latter and treat the patient aggressively rather than wait until the patient meets all the objective criteria for thyroid storm.

Current management/treatment

Patients with thyroid storm must be monitored in the intensive care unit during the initial phases of treatment. Their management includes medications which stop the synthesis (propylthiouracil or methimazole), release (iodine) and peripheral effects of the thyroid hormones (beta-blockers such as propranolol) as well as the high fever (acetaminophen) or hypotension (hydrocortisone). If a precipitating event is present, it should also be treated concurrently. The order of treatment is very important. Propylthiouracil (preferred drug) should be started before iodine in order to prevent stimulation of more thyroid hormone production which could happen if iodine were given initially. Depending on the clinical status of the patient, the two agents may be administered as close as 30-60 minutes apart. Large doses of an antithyroid agent (300 to 400 mg of propylthiouracil every 4 to 6 hours) are given by mouth, by stomach tube, or, if necessary, per rectum. Propylthiouracil is preferable to methimazole because it has the additional action of inhibiting the peripheral generation of T_3 from T_4 in peripheral tissues and in the thyroid itself. Controlling the cardiovascular manifestations of thyroid storm is a vital part of management. Sinus tachycardia, atrial fibrillation, and congestive heart failure are common findings which may occur alone or in combination. Relatively large doses (greater than 160 mg daily) of propranolol are usually required because of the faster metabolism of the drug, and possibly because of an increased number of cardiac beta-adrenergic receptors.

Rationale for therapeutic apheresis

Several alternative agents are reserved for patients with thyroid storm when the first-line therapies outlined above fail or cannot be used due to toxicity. Therapeutic plasma exchange (TPE) is among them, although a variety of drugs should be tried first. TPE becomes an option when clinical deterioration occurs despite the use of first- and/or second-line therapies. Since a portion of T_3 and T_4 is firmly bound to plasma proteins, TPE should, in theory, efficiently reduce their circulating pool. While the literature contains conflicting reports, most patients had a decrease in the hormone concentrations. In one report, TPE increased the elimination of total T_4 approximately 30-fold compared with standard medical treatment. This effect was dependent on the serum level of T_4, suggesting that TPE is more efficient if done early. In patients with amiodarone-associated thyrotoxicosis, TPE has also been used to reduce the plasma concentration of the drug, which has a half-life of months in patients on chronic therapy. TPE in this condition is particularly indicated for patients who have no underlying thyroid disease and develop a drug-induced destructive thyroiditis. In rare cases, TPE is used to render the patient euthyroid prior to thyroidectomy.

Technical notes

Plasma as replacement fluid has the advantage of increasing the concentration of thyroglobulin to bind free thyroid hormone.

Volume treated: 1 to 1.5 TPV
Replacement fluid: albumin; plasma

Frequency: daily or every 2 to 3 days

Duration and discontinuation/number of procedures

TPE should be continued until clinical improvement is noted.

References [769–810]

*As of January 17, 2010 using PubMed and journal published in English language using the search terms thyrotoxicosis, thyroid storm, hyperthyroidism, therapeutic plasma exchange (TPE), and plasmapheresis. References of the identified articles were searched for additional cases and trials.

WILSON'S DISEASE, FULMINANT

Incidence: 3 per 100,000/year in the US				Procedure	Recommendation	Category
				TPE	Grade 1C	I (fulminant hepatic failure with hemolysis)

# of reported patients*: <100

RCT	CT	CS	CR	Type of evidence
0	0	0	16 (17)	Type III

Description of the disease

Autosomal recessive genetic disorder of the ATP7B gene, a copper transporting P-type ATPase protein found in hepatocytes. ATP7B protein deficiency impairs biliary copper excretion, resulting in copper accumulation in the liver, brain, cornea and kidney. The incorporation of copper into ceruloplasmin is also impaired. Patients with Wilson's disease may present with hepatic, neurologic, and/or hematological manifestations. The disease most commonly presents between ages 5-40. Presentation is variable depending on age. In infants and children it is most commonly silent deposit of copper in the liver, teenagers present more with liver disease while adults present with neurological symptoms. The spectrum of liver disease includes asymptomatic liver function tests abnormalities, hepatitis, cirrhosis and acute liver failure. Neurological symptoms include Parkinsonism in most cases, dystonia, cerebellar and pyramidal symptoms. A history of behavioral disturbances is present in half of patients with neurological disease. The appearance of Kayser-Fleischer ring (copper deposits in the outer rim of the cornea) and direct antiglobulin test (DAT) negative hemolytic anemia are relatively common. The hemolysis appears to be primarily due to copper-induced oxidant stress to red cell enzyme pathways and damage to their membrane. No laboratory test is diagnostic but suggestive results include low serum ceruloplasmin, increase 24-hour urinary copper excretion, elevated serum copper. The ''gold standard'' for diagnosis remains liver biopsy with elevated copper.

Current management/treatment

Low-copper diets are recommended. Zinc acetate stimulates metallothioneine. This protein in intestinal mucosal cells reduces absorption of both dietary copper as well as copper in the enterohepatic circulation. Zinc has proven efficacy for this disease and is essentially nontoxic. For patients with hepatitis or cirrhosis, but without evidence of hepatic decompensation or neurologic/psychiatric symptoms, it is the therapy of choice. Zinc is also first choice for maintenance therapy and in presymptomatic, pediatric and pregnant patients. All asymptomatic patients should be treated prophylactically, since the disease is close to 100% penetrant. Urinary excretion can be increased by chelation therapy with penicillamine or with trientine. Penicillamine used to be the primary copper chelator agent; however currently plays a minor role because of its toxicity. If penicillamine is given, it should always be accompanied by 25 mg/day of pyridoxine. Trientine is a less toxic chelator and can replace penicillamine when a chelator is indicated. Those chelators can be used as temporizing agents to treat enormous release of copper into the blood stream in fulminant hepatic failure with renal failure; however substantial removal is not achieved for at least 1-3 months. Other methods have been used to reduce copper load in an attempt to stabilize patients. Those methods have included hemofiltration, albumin dialysis and the Molecular Adsorbents Recirculating System (MARS).

Liver transplantation is the mainstay of therapy for patients with severe hepatic failure. The severity is estimated using prognostic score which is based on combination of laboratory values, most commonly serum bilirubin, serum aspartate transferase (AST) and coagulation status (INR/PT). Liver transplantation reverses most of the clinical and biochemical pathological manifestations of the disease within a few months. For initial neurologic therapy, tetrathiomolybdate is emerging as the drug of choice because of its rapid action, preservation of neurologic function, and low toxicity. Penicillamine and trientine should be avoided since they often worsen neurologic disease if used as initial therapy. Anticopper therapy must be lifelong.

Rationale for therapeutic apheresis

Rarely, Wilson's disease can present as fulminant hepatic failure with necrotic hepatocytes releasing free copper into the serum. The hypercuperemia leads to severe DAT-negative hemolysis and acute renal failure (secondary to the hypercuperemia and the intravascular hemolysis). This syndrome is associated with rapid clinical deterioration and is nearly always fatal without liver transplantation. However, donor organs for liver transplantation are not always available and temporizing treatments must be aimed at treating the damage caused by the release of the massive amounts of copper into the circulation. Since there is no alternative method to rapidly lowering serum copper level, TPE can be beneficial in this scenario as it can rapidly remove significant amount of copper. Decreased serum copper would decrease hemolysis, prevent progression of renal failure and provide clinical stabilization. Thus, in most reported cases, TPE was used as a bridge to liver transplantation. In addition, the widespread availability of TPE over MARS or equivalent technology makes it a more reasonable choice of therapy.

Technical notes

Replacement of the patient's plasma with fresh frozen plasma provides additional coagulation factors and rapidly corrects coagulopathy. A combination of plasma and albumin is also possible. Use of albumin alone will worsen coagulopathy.

Volume treated: 1 to 1.5 TPV	**Frequency:** daily
Replacement fluid: plasma	

Duration and discontinuation/number of procedures

The reduction in serum copper in most case reports had been achieved rapidly. The specific laboratory tests for the disease e.g. serum copper, 24-hour urinary copper excretion are not easily available hence are not helpful in measuring effectiveness and guiding the frequency of the treatment. In most cases therapeutic plan might be based on clinical parameters and routine testing such as improved encephalopathy, controlled hemolysis, decrease in liver function tests abnormalities, etc.

References [811–815]

*As of September 15, 2009 using PubMed and the MeSH search terms Wilson's disease and TPE, plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

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